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| (54) Title: SUBSTITUTED SULFONYLALKANOYLAMINO HYDROXYETHYLAMINO SULFONAMIDE RETROVIRAL PROTEASE INHIBITORS | | |
| (57) Abstract <p>Selected sulfonylalkanoylamino hydroxyethylamino sulfonamide compounds are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease. The present invention relates to such retroviral protease inhibitors and, more particularly, relates to selected novel compounds, composition and method for inhibiting retroviral proteases, such as human immunodeficiency virus (HIV) protease, prophylactically preventing retroviral infection or the spread of a retrovirus, and treatment of a retroviral infection.</p> | | |

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SUBSTITUTED SULFONYLALKANOYLAMINO HYDROXYETHYLAMINO
SULFONAMIDE RETROVIRAL PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

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The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds, composition and method for inhibiting retroviral proteases, such as human immunodeficiency virus (HIV) protease. This invention, in particular, relates to sulfonylalkanoylamino hydroxyethylamino sulfonamide protease inhibitor compounds, composition and method for inhibiting retroviral proteases, prophylactically preventing retroviral infection or the spread of a retrovirus, and treatment of a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

20

During the replication cycle of retroviruses, gag and gag-pol gene transcription products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virions. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed mutagenesis of an aspartic acid residue in the HIV protease active site that processing of the gag precursor protein is prevented. Thus, attempts have been made to

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inhibit viral replication by inhibiting the action of retroviral proteases.

5 Retroviral protease inhibition typically involves a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds (typically in a reversible manner) to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit specific processing of structural proteins and the release of
10 retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for
15 inhibition of HIV protease. WO 92/08701, WO 93/23368, WO 93/23379, WO 94/04493, WO 94/10136 and WO 94/14793 (each of which is incorporated herein by reference in its entirety) for example describe sulfonylalkanoylamino hydroxyethylamine, sulfonylalkanoylamino
20 hydroxyethylurea, sulfonylalkanoylamino hydroxyethyl sulfonamide and sulfonylalkanoylamino hydroxyethylaminosulfonamide isostere containing retroviral protease inhibitors. Other such compounds include hydroxyethylamine isosteres and reduced amide
25 isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1
30 Protease," Science, 249, 527 (1990). US 5,157,041, WO 94/04491, WO 94/04492, WO 94/05639 and US Patent Application Serial No. 08/294,468, filed August 23, 1994, (each of which is incorporated herein by reference in its entirety) for example describe hydroxyethylamine,
35 hydroxyethylurea or hydroxyethyl sulfonamide isostere containing retroviral protease inhibitors.

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. EP 468 641 discloses renin inhibitors and intermediates for the preparation of the inhibitors, which include sulfonamide-containing hydroxyethylamine compounds, such as 3-(t-butoxycarbonyl)amino-cyclohexyl-1-(phenylsulfonyl)amino-2(5)-butanol. G.B. 2,200,115 also discloses sulfamoyl-containing hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfonamide-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally are not predictive for effective HIV protease inhibition.

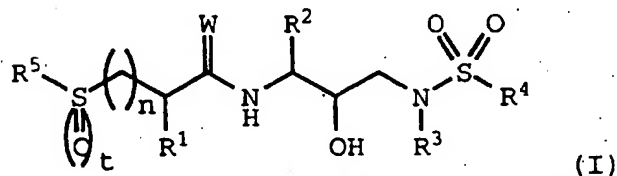
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BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to selected retroviral protease inhibitor compounds, analogs and pharmaceutically acceptable salts, esters and prodrugs thereof. The subject compounds are characterized as sulfonylalkanoylamino hydroxyethylamino sulfonamide inhibitor compounds. The invention compounds advantageously inhibit retroviral proteases, such as human immunodeficiency virus (HIV) protease. Therefore, this invention also encompasses pharmaceutical compositions, methods for inhibiting retroviral proteases and methods for treatment or prophylaxis of a retroviral infection, such as an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is
 5 provided a retroviral protease inhibiting compound of the
 formula:



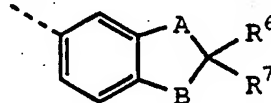
10 or a pharmaceutically acceptable salt, prodrug or ester
 thereof, wherein n and t each independently represent 0,
 1 or 2; preferably n represents 1 and t represents 1 or
 2;

15 W represents O or S; preferably, W represents O;

R¹ represents hydrogen, alkyl, alkenyl, alkynyl,
 hydroxyalkyl, alkoxyalkyl, cyanoalkyl, -CH₂CONH₂,
 -CH₂CH₂CONH₂, -CH₂S(O)₂NH₂, -CH₂SCH₃, -CH₂S(O)CH₃ or
 20 -CH₂S(O)₂CH₃ radicals; preferably, R¹ represents hydrogen,
 alkyl of 1-5 carbon atoms, alkenyl of 2-5 carbon atoms,
 alkynyl of 2-5 carbon atoms, hydroxyalkyl of 1-3 carbon
 atoms, alkoxyalkyl of 1-3 alkyl and 1-3 alkoxy carbon atoms,
 cyanoalkyl of 1-3 alkyl carbon atoms, -CH₂CONH₂,
 25 -CH₂CH₂CONH₂, -CH₂S(O)₂NH₂, -CH₂SCH₃, -CH₂S(O)CH₃ or
 -CH₂S(O)₂CH₃ radicals; more preferably, R¹ represents
 hydrogen, alkyl of 1-3 carbon atoms, alkenyl of 2-3 carbon
 atoms, alkynyl of 2-3 carbon atoms or cyanomethyl radicals;
 even more preferably, R¹ represents hydrogen, methyl, ethyl
 30 or cyanomethyl radicals; yet more preferably, R¹ represents
 methyl or ethyl radicals; and most preferably, R¹ represents
 a methyl radical;

- R² represents alkyl, aralkyl, alkylthioalkyl, arylthioalkyl or cycloalkylalkyl radicals; preferably, R² represents radicals of alkyl of 1-5 carbon atoms, aralkyl of 1-3 alkyl carbon atoms, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthioalkyl of 1-3 alkyl carbon atoms or cycloalkylalkyl of 1-3 alkyl carbon atoms and 3-6 ring member carbon atoms; more preferably, R² represents radicals of alkyl of 3-5 carbon atoms, arylmethyl, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthiomethyl or cycloalkylmethyl of 5-6 ring member carbon atoms radicals; even more preferably, R² represents isobutyl, n-butyl, CH₃SCH₂CH₂-, benzyl, phenylthiomethyl, (2-naphthylthio)methyl, 4-methoxy phenylmethyl, 4-hydroxyphenylmethyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals; even more preferably, R² represents benzyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals; most preferably, R² represents benzyl radical;
- R³ represents alkyl, cycloalkyl or cycloalkylalkyl radicals; preferably, R³ represents radicals of alkyl radical of 1-5 carbon atoms, cycloalkyl of 5-8 ring members or cycloalkylmethyl radical of 3-6 ring members; more preferably, R³ represents propyl, isoamyl, isobutyl, butyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl or cycloheptyl radicals; more preferably R³ represents isobutyl or cyclopentylmethyl radicals;
- R⁴ represents aryl, heteroaryl or heterocyclo radicals; preferably, R⁴ represents aryl, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals; or

R⁴ represents a radical of the formula



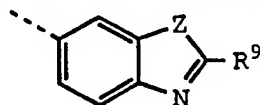
wherein A and B each independently represent O, S, SO or SO₂; preferably, A and B each represent O;

R⁶ represents deuterium, alkyl or halogen radicals;

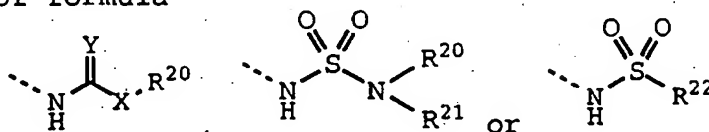
- 5 preferably, R⁶ represents deuterium, alkyl of 1-5 carbon atoms, fluoro or chloro radicals; more preferably R⁶ represents deuterium, methyl, ethyl, propyl, isopropyl or fluoro radicals;

- 10 R⁷ represents hydrogen, deuterium, alkyl or halogen radicals; preferably, R⁷ represents hydrogen, deuterium, alkyl of 1-3 carbon atoms, fluoro or chloro radicals; more preferably, R⁷ represents hydrogen, deuterium, methyl or fluoro radicals; or R⁶ and R⁷ each independently represent
15 fluoro or chloro radicals; and preferably, R⁶ and R⁷ each represent a fluoro radical; or

R⁴ represents a radical of the formula



- 20 wherein Z represents O, S or NH; and R⁹ represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR²¹;

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R²⁰ represents radicals of hydrogen, alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, heterocycloalkyl, aminoalkyl, N-mono-substituted or N,N-disubstituted aminoalkyl wherein said substituents are alkyl, aralkyl,
30 carboxyalkyl, alkoxycarbonylalkyl, cyanoalkyl or hydroxyalkyl radicals; preferably, R²⁰ represents radicals of hydrogen, alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms, alkynyl of 2 to 5 carbon atoms, aralkyl of 1 to 5 alkyl carbon atoms, heteroaralkyl of 5 to 6 ring

members and 1 to 5 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 5 alkyl carbon atoms, aminoalkyl of 2 to 5 carbon atoms, N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 5 alkyl carbon atoms
5 wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms, aralkyl of 1 to 3 alkyl carbon atoms radicals, carboxyalkyl of 1 to 5 carbon atoms, alkoxycarbonylalkyl of 1 to 5 alkyl carbon atoms, cyanoalkyl of 1 to 5 carbon atoms or hydroxyalkyl of 2 to
10 5 carbon atoms; more preferably, R^{20} represents radicals of hydrogen, alkyl of 1 to 5 carbon atoms, phenylalkyl of 1 to 3 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 3 alkyl carbon atoms, or N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 3
15 carbon atoms wherein said substituents are alkyl radicals of 1 to 3 carbon atoms; and most preferably, R^{20} represents hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, 2-(1-pyrrolidinyl)ethyl, 2-(1-piperidinyl)ethyl, 2-(1-piperazinyl)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 2-(4-morpholinyl)ethyl, 2-(4-thiomorpholinyl)ethyl or 2-(N,N-dimethylamino)ethyl radicals; or

XR^{20} represents radicals of hydroxymethyl, aminomethyl, N-
25 mono-substituted or N,N-disubstituted aminomethyl wherein said substituents are alkyl, aralkyl, carboxyalkyl, alkoxycarbonylalkyl, cyanoalkyl or hydroxyalkyl radicals; preferably, XR^{20} represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted
30 aminomethyl wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms, aralkyl of 1 to 3 alkyl carbon atoms, carboxyalkyl of 1 to 5 carbon atoms, alkoxycarbonylalkyl of 1 to 5 alkyl carbon atoms, cyanoalkyl of 1 to 5 carbon atoms or hydroxyalkyl of 2 to
35 5 carbon atoms; more preferably, XR^{20} represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted aminomethyl wherein said substituents are

radicals of alkyl of 1 to 3 carbon atoms; and most preferably, XR^{20} represents hydroxymethyl or aminomethyl radicals;

- 5 R^{21} represents hydrogen or alkyl radicals; preferably, R^{21} represents hydrogen radical or alkyl radical of 1 to 3 carbon atoms; more preferably, R^{21} represents hydrogen or methyl radicals; and most preferably, R^{21} represents a hydrogen radical; or

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the radical of formula $-NR^{20}R^{21}$ represents a heterocyclo radical; preferably, the radical of formula $-NR^{20}R^{21}$ represents a 5 to 6 ring member heterocyclo radical; more preferably, the radical of formula $-NR^{20}R^{21}$ represents
15 pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, morpholinyl or thiomorpholinyl radicals; and

- R^{22} represents alkyl or $R^{20}R^{21}N$ -alkyl radicals;
20 preferably, R^{22} represents alkyl or $R^{20}R^{21}N$ -alkyl radicals wherein alkyl is 1 to 3 carbon atoms; and more preferably, R^{22} represents alkyl radical of 1 to 3 carbon atoms; and

- preferably R^4 represents phenyl, 2-naphthyl, 4-
25 methoxyphenyl, 4-hydroxyphenyl, 3,4-dimethoxyphenyl, 3-aminophenyl, 4-aminophenyl, benzothiazol-5-yl, benzothiazol-6-yl, 2-amino-benzothiazol-5-yl, 2-(methoxycarbonylamino)benzothiazol-5-yl, 2-amino-benzothiazol-6-yl, 2-(methoxycarbonylamino) benzothiazol-
30 6-yl, 5-benzoxazolyl, 6-benzoxazolyl, 6-benzopyranyl, 3,4-dihydrobenzopyran-6-yl, 7-benzopyranyl, 3,4-dihydrobenzopyran-7-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-
35 dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 5-benzimidazolyl, 2-(methoxycarbonylamino)benzimidazol-5-yl, 6-quinolinyl,

7-quinolinyl, 6-isoquinolinyl or 7-isoquinolinyl radicals; more preferably, R⁴ represents phenyl, 2-naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2-(methoxycarbonylamino) benzothiazol-5-yl, 2-(methoxycarbonylamino)benzothiazol-6-yl or 2-(methoxycarbonylamino)benzimidazol-5-yl radicals; and most preferably, R⁴ represents phenyl, 4-methoxyphenyl, 4-hydroxyphenyl, benzothiazol-5-yl, benzothiazol-6-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2-(methoxycarbonylamino)benzothiazol-6-yl or 2-(methoxycarbonylamino)benzimidazol-5-yl radicals; and

R⁵ represents heteroaryl or heterocyclo radicals each of which is coupled via a ring carbon atom; or alkyl radical substituted with R¹⁰, cycloalkylamino, aralkylamino, aminoalkoxycarbonyl, (alkylamino)alkoxycarbonyl, (dialkylamino)alkoxycarbonyl, (aminocarbonyl)(alkoxycarbonyl)methyl or bis(aminocarbonyl)methyl radicals, or 1 or more radicals of amino, alkylamino or dialkylamino, or 2 or more radicals of hydroxy or alkoxy radicals;

preferably, R⁵ represents 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals each of which is coupled via a ring carbon atom; or alkyl radical of 3-8 carbon atoms substituted with 2-5 radicals of hydroxy or alkoxy of 1-3

carbon atoms or 2-3 radicals of amino, alkylamino of 1-3 carbon atoms or dialkylamino of 1-3 alkyl carbon atoms; or alkyl radical of 1-5 carbon atoms substituted with R¹⁰; or alkyl radical of 2-4 carbon atoms substituted with radicals of amino, alkylamino of 1-3 carbon atoms, dialkylamino of 1-3 alkyl carbon atoms, cycloalkylamino of 3-6 ring carbon atoms, aralkylamino of 1-3 alkyl carbon atoms, aminoalkoxycarbonyl of 2-5 alkoxy carbon atoms, (alkylamino)alkoxycarbonyl of 1-3 alkyl carbon atoms and 2-5 alkoxy carbon atoms, (dialkylamino)alkoxycarbonyl of 1-3 alkyl carbon atoms and of 2-5 alkoxy carbon atoms, (aminocarbonyl)(alkoxycarbonyl)methyl of 1-3 alkoxy carbon atoms or bis(aminocarbonyl)methyl radicals;

more preferably, R⁵ represents a 5 to 6 ring member heteroaryl radical which is coupled via a ring carbon atom, or alkyl radical of 1-5 carbon atoms substituted with R¹⁰, or alkyl radical of 3-8 carbon atoms substituted with 2-5 hydroxy radicals;

R¹⁰ represents heteroaryl, heterocyclo, alkoxycarbonyl, arylcarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl or heterocyclocarbonyl radicals;

preferably, R¹⁰ represents alkoxycarbonyl of 1-5 alkoxy carbon atoms, arylcarbonyl, 3-6 ring membered cycloalkylcarbonyl, benzo fused 3-6 ring membered cycloalkylcarbonyl, 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl, benzo fused 5 to 6 ring member heterocyclo, 5 to 6 ring member heteroarylcarbonyl, 5 to 6 ring member heterocyclocarbonyl, benzo fused 5 to 6 ring member heteroarylcarbonyl or benzo fused 5 to 6 ring member heterocyclocarbonyl radicals;

more preferably, R¹⁰ represents alkoxy carbonyl of 1-4 alkoxy carbon atoms, aryl carbonyl, 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl, 5 to 6 ring member heteroaryl carbonyl or 5 to 6 ring member heterocyclocarbonyl radicals;

most preferably, R¹⁰ represents ethoxycarbonyl, tert-butoxycarbonyl, benzoyl, naphthoyl, aminophenyl carbonyl, amidinophenyl carbonyl, pyridyl carbonyl, thiazolyl carbonyl, imidazolyl carbonyl, pyrazolyl carbonyl, pyrimidinyl carbonyl, pyrazinyl carbonyl, benzimidazolyl carbonyl, indolyl carbonyl, pyrrolyl carbonyl, quinolinyl carbonyl, pyrrolidiny carbonyl, 1-(benzyloxycarbonyl)pyrrolidinyl carbonyl, piperidinyl carbonyl, 1-(benzyloxycarbonyl)piperidinyl carbonyl, piperazinyl carbonyl, 4-methylpiperazinyl carbonyl, 4-benzylpiperazinyl carbonyl, 4-(tert-butoxycarbonyl)piperazinyl carbonyl, morpholinyl carbonyl, thiomorpholinyl carbonyl, 1,1-dioxothiomorpholinyl carbonyl, pyrrolidinyl, 1-oxopyrrolidin-1-yl, 1-(benzyloxycarbonyl)pyrrolidinyl, piperidinyl, 1-oxopiperidin-1-yl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, 4-(tert-butoxycarbonyl)piperazinyl, morpholinyl, 4-oxomorpholin-4-yl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, 1,1,4-trioxothiomorpholin-4-yl, thiazolyl, oxazolyl, pyrrolyl, furyl, imidazolyl, pyrazolyl, isoxazolyl, thienyl, pyrimidinyl, pyrazinyl, pyridyl, quinolinyl, quinolonyl, N-methylquinolonyl, benzothiazolyl, benzoxazolyl, benzofuranyl, benzimidazolyl, indolyl, dihydroxytetrahydrofuran-5-yl, trihydroxytetrahydrofuran-5-yl, 2-methoxydihydroxytetrahydrofuran-5-yl, trihydroxytetrahydrofuranyl, 2-(hydroxymethyl)dihydroxytetrahydrofuran-5-yl, 2-

methoxytrihydroxytetrahydropyran-6-yl or tetrahydroxytetrahydropyran-6-yl radicals; or

R¹⁰ represents R¹¹R¹²N-C(O)- radical, wherein

5

R¹¹ represents heteroaryl, heterocyclo, heteroaralkyl, heterocycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cycloalkylaminoalkyl, aralkylaminoalkyl or diaminoalkyl radicals; preferably,

10 R¹¹ represents 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals, or alkyl radical of 1-5 carbon atoms

15 substituted with 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals, or alkyl radical of 2-4 carbon atoms

substituted with radicals of amino, alkylamino of 1-3 carbon atoms, dialkylamino of 1-3 alkyl carbon atoms, cycloalkylamino of 3-6 ring carbon atoms or aralkylamino of 1-3 alkyl carbon atoms, or diaminoalkyl radical of 3-5 carbon atoms; more preferably, R¹¹ represents alkyl

20 radical of 1-3 carbon atoms substituted with 5 to 6 ring member heteroaryl or 5 to 6 ring member heterocyclo radicals; even more preferably, R¹¹ represents alkyl radical of 1-3 carbon atoms substituted with

pyrrolidinyl, 1-oxopyrrolidin-1-yl, piperidinyl, 1-oxopiperidin-1-yl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, 4-(tert-butoxycarbonyl)piperazinyl, morpholinyl, 4-oxomorpholin-4-yl, thiomorpholinyl, 1,1-dioxothiomorpholinyl or 1,1,4-trioxothiomorpholin-4-yl

30 radicals; most preferably, R¹¹ represents 2-pyrrolidinylmethyl, 2-(1-pyrrolidinyl)ethyl, 2-(1-oxopyrrolidin-1-yl)ethyl, 2-(1-piperidinyl)ethyl, 2-(1-oxopiperidin-1-yl)ethyl, 2-(4-morpholinyl)ethyl, 2-(4-oxomorpholin-4-yl)ethyl, 2-(4-thiomorpholinyl)ethyl, 2-(1,1-dioxothiomorpholin-4-yl)ethyl, 2-(1,1,4-

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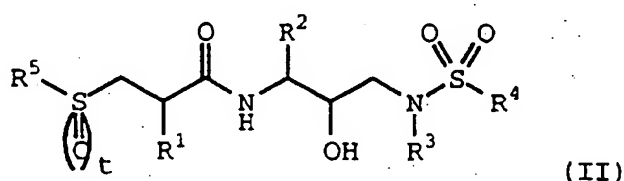
trioxothiomorpholin-4-yl)ethyl or 1,3-diaminoprop-2-yl radicals; and

- R¹² represents hydrogen or alkyl radicals; preferably,
- 5 R¹² represents radicals of hydrogen or alkyl of 1-3 carbon atoms; more preferably, R¹² represents hydrogen or methyl radicals; most preferably, R¹² represents a hydrogen radical;
- 10 more preferably, R⁵ represents 2-pyridyl, ethoxycarbonylpropyl, benzoylmethyl, morpholinylcarbonylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylmethyl, piperazinylcarbonylmethyl, 4-(tert-
- 15 butoxycarbonyl)piperazinylcarbonylethyl, piperazinylcarbonylethyl, thiomorpholinylcarbonylmethyl, 1,1-dioxothiomorpholinylcarbonylmethyl, imidazolylethyl, imidazolylcarbonylmethyl, pyrazolylethyl, thiazolylethyl, imidazolylmethyl, pyrazolylmethyl, thiazolylmethyl,
- 20 benzimidazolylmethyl, pyridylethyl, pyridylcarbonylmethyl, pyrrolidinylmethyl, 1-(benzyloxycarbonyl)pyrrolidinylmethyl, 5-methoxy-3,4-dihydroxy-tetrahydrofuranylethyl, N-[2-(4-oxomorpholin-4-yl)ethyl]aminocarbonylmethyl, N-[2-(1-
- 25 pyrrolidinyl)ethyl]aminocarbonylmethyl, N-[2-(1-pyrrolidinyl)ethyl]aminocarbonylethyl, N-[2-(1-oxopyrrolidin-1-yl)ethyl]aminocarbonylmethyl, 2,2-bis(hydroxymethyl)ethyl, 2,2,2-tris(hydroxymethyl)ethyl, 2-[(2-aminoethyl)aminocarbonyl]ethyl or 2-[(2-
- 30 (methylamino)ethyl)aminocarbonyl]ethyl radicals; and most preferably, R⁵ represents benzoylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylethyl, piperazinylcarbonylethyl, imidazolylethyl,
- 35 pyrazolylethyl, thiazolylethyl, imidazolylmethyl, pyrazolylmethyl, thiazolylmethyl, pyridylethyl,

pyridylcarbonylmethyl, pyrrolidinylmethyl or 1-(benzyloxycarbonyl)pyrrolidinylmethyl radicals.

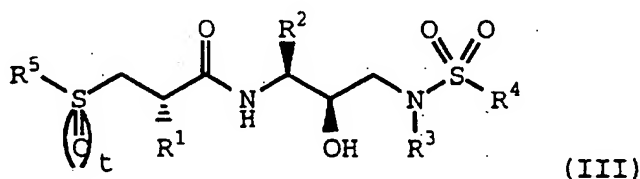
Preferably, the absolute stereochemistry of the carbon atom of -CH(OH)- group is (R) and the absolute stereochemistry of the carbon atoms of -CH(R¹)- and -CH(R²)- groups is (S).

A family of compounds of particular interest within Formula I are compounds embraced by the formula



or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein t, R¹, R², R³, R⁴ and R⁵ are as defined above.

A family of compounds of further interest within Formula II are compounds embraced by the formula



or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein t, R¹, R², R³, R⁴ and R⁵ are as defined above.

Compounds of interest include the following:

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

5

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

10 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

15 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

20 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;

25 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;

30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;

35 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;

5 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;

10 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;

15 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;

20 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;

25 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;

30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;

35 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;

- N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;
- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;

5 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;

10 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;

15 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;

20 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;

25 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;

30 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;

35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;

- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-benzoyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;

5

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;

10

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;

15

N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;

20

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;

25

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;

30

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;

35

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;

- N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl)sulfonyl]propanamide;

5 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl)sulfonyl]propanamide;

10 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;

15 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;

20 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;

25 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide; and

N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide.

30 As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing preferably from 1 to 8 carbon atoms, more preferably from 1 to 5 carbon atoms, most preferably 1-3 carbon atoms. Examples of such radicals
35 include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like. The term "hydroxyalkyl", alone or in

combination, means an alkyl radical as defined above wherein at least one hydrogen radical is replaced with a hydroxyl radical, preferably 1-3 hydrogen radicals are replaced by hydroxyl radicals, more preferably, 1-2
5 hydrogen radicals are replaced by hydroxyl radicals, and most preferably, one hydrogen radical is replaced by a hydroxyl radical. The term "alkenyl", alone or in combination, means a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and
10 containing preferably from 2 to 8 carbon atoms, more preferably from 2 to 5 carbon atoms, most preferably from 2 to 3 carbon atoms. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. The term "alkynyl", alone
15 or in combination, means a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing preferably from 2 to 8 carbon atoms, more preferably from 2 to 5 carbon atoms, most preferably from 2 to 3 carbon atoms. Examples of alkynyl radicals
20 include ethynyl, propynyl (propargyl), butynyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy,
25 iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains preferably from 3 to 8 carbon atom ring members,
30 more preferably from 3 to 7 carbon atom ring members, most preferably from 5 to 6 carbon atom ring members, and which may optionally be a benzo fused ring system which is optionally substituted as defined herein with respect to the definition of aryl. Examples of such cycloalkyl
35 radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and

"tricyclic" as used herein are intended to include both fused ring systems, such as naphthyl and β -carbolinyl, and substituted ring systems, such as biphenyl, phenylpyridyl, naphthyl and diphenylpiperazinyl. The

5 term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical as defined above. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl,

10 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, cyclohexylbutyl and the like. The term "benzo", alone or in combination, means the divalent radical $C_6H_4=$ derived from benzene. The term "aryl", alone or in combination, means a phenyl

15 or naphthyl radical which is optionally substituted with one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl, carboxy, alkoxycarbonyl, cycloalkyl, heterocyclo, alkanoylamino, amido, amidino, alkoxycarbonylamino, N-

20 alkylamidino, alkylamino, dialkylamino, N-alkylamido, N,N-dialkylamido, aralkoxycarbonylamino, alkylthio, alkylsulfinyl, alkylsulfonyl and the like. Examples of aryl radicals are phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-CF₃-

25 phenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-

30 hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl, piperazinylphenyl and the like. The terms "aralkyl" and "aralkoxy", alone or in combination, means an alkyl or alkoxy radical as

35 defined above in which at least one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, benzyloxy, 2-phenylethyl, dibenzylmethyl,

- hydroxyphenylmethyl, methylphenylmethyl, diphenylmethyl, diphenylmethoxy, 4-methoxyphenylmethoxy and the like. The term "aralkoxycarbonyl", alone or in combination, means a radical of the formula aralkyl-O-C(O)- in which
- 5 the term "aralkyl" has the significance given above. Examples of an aralkoxycarbonyl radical are benzyloxycarbonyl and 4-methoxyphenylmethoxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above.
- 10 The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl radical of the formula
- 15 cycloalkyl-C(O)- in which the term "cycloalkyl" has the significance give above, such as cyclopropylcarbonyl, cyclohexylcarbonyl, adamantylcarbonyl, 1,2,3,4-tetrahydro-2-naphthoyl, 2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl, 1-hydroxy-1,2,3,4-tetrahydro-6-naphthoyl and
- 20 the like. The term "aralkanoyl" means an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like. The term "aroyl"
- 25 means an acyl radical derived from an arylcarboxylic acid, "aryl" having the meaning given above. Examples of such aroyl radicals include substituted and unsubstituted benzoyl or naphthoyl such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The term "heteroatoms" means
- 30 nitrogen, oxygen and sulfur heteroatoms. The terms "heterocyclo," alone or in combination, means a saturated or partially unsaturated monocyclic, bicyclic or

tricyclic heterocycle radical containing at least one, preferably 1 to 4, more preferably 1 to 2, nitrogen, oxygen or sulfur atom ring member and having preferably 3 to 8 ring members in each ring, more preferably 3 to 7 ring members in each ring and most preferably 5 to 6 ring members in each ring. "Heterocyclo" is intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems. Such heterocyclo radicals may be optionally substituted on at least one, preferably 1 to 4, more preferably 1 to 3, most preferably 1 to 2, carbon atoms by halogen, alkyl, alkoxy, hydroxy, oxo, aryl, aralkyl, heteroaryl, heteroaralkyl, amidino, N-alkylamidino, alkoxycarbonylamino, alkylsulfonylamino and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by hydroxy, alkyl, aralkoxycarbonyl, alkanoyl, alkoxycarbonyl, heteroaralkyl, phenyl or phenylalkyl and/or on a tertiary nitrogen atom (i.e., =N-) by oxido. "Heterocycloalkyl" means an alkyl radical as defined above in which at least one hydrogen atom is replaced by a heterocyclo radical as defined above, such as pyrrolidinylmethyl, tetrahydrothienylmethyl, pyridylmethyl and the like. The term "heteroaryl", alone or in combination, means an aromatic heterocyclo radical as defined above, which is optionally substituted as defined above with respect to the definitions of aryl and heterocyclo. Examples of such heterocyclo and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, (e.g., 2-(1-piperidinyl)pyridyl and 2-(4-benzyl piperazin-1-yl-1-pyridinyl, etc.), pyrazinyl, pyrimidinyl, furyl, tetrahydrofuryl, thienyl, tetrahydrothienyl and its sulfoxide and sulfone derivatives, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 1-oxido-2-quinolinyl, quinolin-2-onyl,

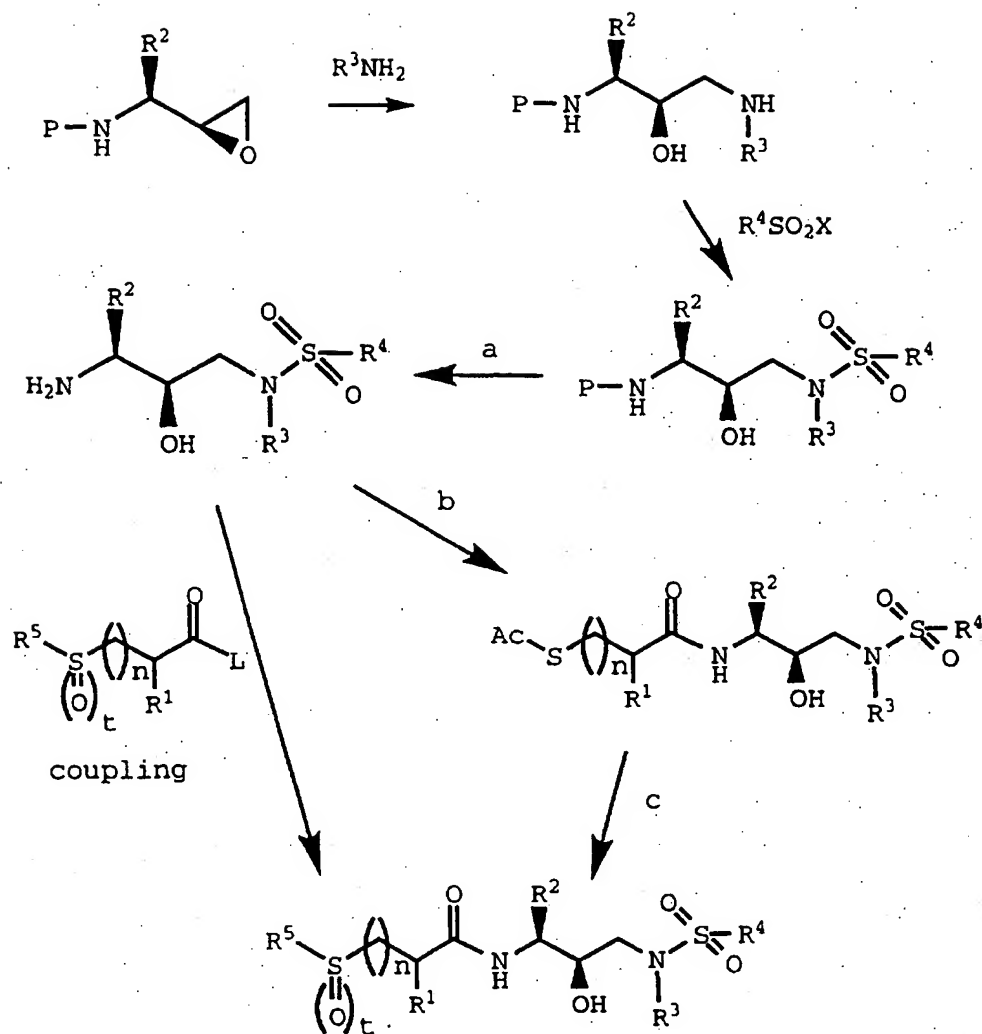
etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), quinoxalinyl, 5 β -carbolinyl, 2-benzofurancarbonyl, 1-,2-,4- or 5-benzimidazolyl, methylenedioxyphen-4-yl, methylenedioxyphen-5-yl, ethylenedioxyphenyl, benzothiazolyl, benzopyranyl, benzofuryl, 2,3-10 dihydrobenzofuryl, benzoxazolyl and the like. The term "heteroaralkyl", alone or in combination, means an alkyl radical as defined above in which at least one hydrogen atom is replaced by an heteroaryl radical as defined above, such as benzofurylmethyl, 3-furylpropyl, 15 quinolinylmethyl, 2-thienylethyl, pyridylmethyl, 2-pyrrolylpropyl, 1-imidazolylethyl and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the 20 meaning given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the meaning given above. The term "heterocycloalkoxycarbonyl" means an acyl group derived from heterocycloalkyl-O-COOH wherein heterocycloalkyl is as defined above. The term "heterocycloalkanoyl" is an 25 acyl radical derived from a heterocycloalkylcarboxylic acid wherein heterocyclo has the meaning given above. The term "heterocycloalkoxycarbonyl" means an acyl radical derived from a heterocycloalkyl-O-COOH wherein 30 heterocyclo has the meaning given above. The term "heteroaryloxy carbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the meaning given above. The term "aminocarbonyl" alone or in combination, means an amino-35 substituted carbonyl (carbamoyl) group wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from alkyl, aryl,

aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkylcarboxylic acid wherein the amino group can be a primary, secondary or
5 tertiary amino group containing substituents selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the meaning as
10 defined above wherein one or more hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term "leaving group" (L or W) generally
15 refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides,
20 triflates, tosylates and the like. Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that the general
25 procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable to those compounds of
30 opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be
35 inverted to the (S) stereochemistry using well-known methods.

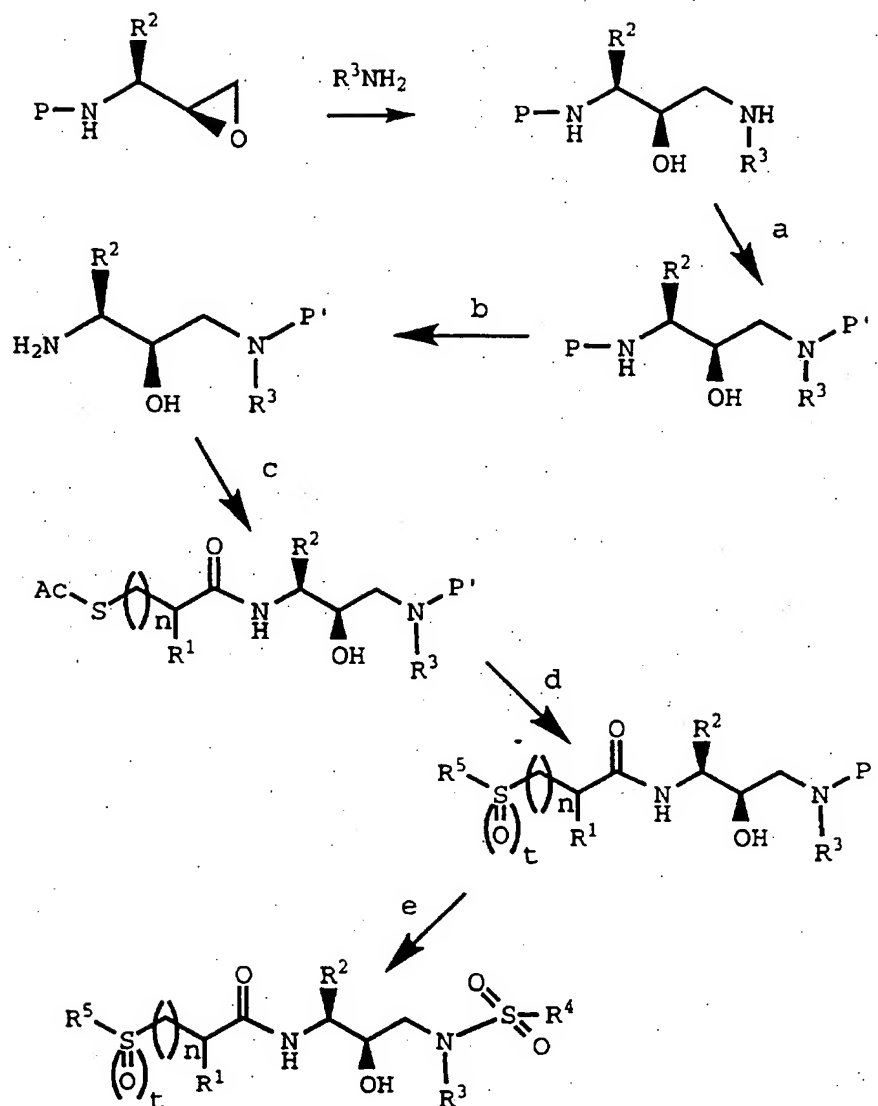
Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedures as schematically shown in Schemes I and II.

SCHEME I

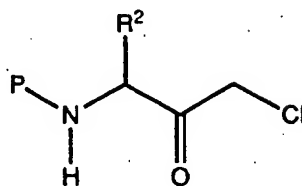
a) deprotection; $X = Cl$ or Br ;

b) $AcS(CH_2)_nCH(R^1)CO_2H$ coupling; c) hydrolysis, R^5L displacement, oxidation.

SCHEME II

a) protection; b) selective deprotection;
 c) $AcS(CH_2)_nCH(R^1)CO_2H$ coupling; d) hydrolysis,
 R^5L displacement, oxidation; e) deprotection,
 R^4SO_2X coupling ($X = Cl$ or Br).

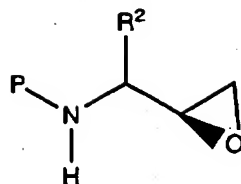
An N-protected chloroketone derivative of an amino acid having the formula:



5 wherein P represents an amino protecting group, and R² is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include
10 carbobenzoxo, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxo. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The
15 reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as
20 from Bachem, Inc., Torrance, California. Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

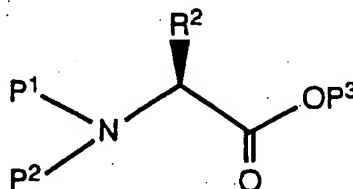
25 The halo alcohol can be utilized directly, as described below, or, preferably, is reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of
30 the formula:

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wherein P and R² are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared, such as in co-owned and co-pending PCT Patent Application Serial No. PCT/US93/04804 (WO 93/23388) and PCT/US94/12201, and US Patent Application Attorney Docket No. C-2860, each of which is incorporated herein by reference in their entirety) disclose methods of preparing chiral epoxide, chiral cyanohydrin, chiral amine and other chiral intermediates useful in the preparation of retroviral protease inhibitors, starting with a DL-, D- or L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected amino acid ester. For the purposes of illustration, a protected L-amino acid with the following formula will be used to prepare the inhibitors of this invention:



wherein P^3 represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl, 4-methoxyphenylmethyl and the like; R^2 is as defined above; and P^1 and P^2 independently are selected from amine protecting groups, including but not limited to, aralkyl, substituted aralkyl, cycloalkenylalkyl and substituted cycloalkenylalkyl, allyl, substituted allyl, acyl, alkoxycarbonyl, aralkoxycarbonyl and silyl. Examples of aralkyl include, but are not limited to benzyl, ortho-methylbenzyl, trityl and benzhydryl, which can be optionally substituted with halogen, alkyl of C_1 - C_8 , alkoxy, hydroxy, nitro, alkylene, amino, alkylamino, acylamino and acyl, or their salts, such as phosphonium and ammonium salts. Examples of aryl groups include phenyl, naphthalenyl, indanyl, anthracenyl, durenyl, 9-(9-phenylfluorenyl) and phenanthrenyl, cycloalkenylalkyl or substituted cycloalkenylalkyl radicals containing cycloalkyls of C_6 - C_{10} . Suitable acyl groups include carbobenzoxy, t-butoxycarbonyl, iso-butoxycarbonyl, benzoyl, substituted benzoyl, butyryl, acetyl, trifluoroacetyl, tri-chloroacetyl, phthaloyl and the like. Preferably P^1 and P^2 are independently selected from aralkyl and substituted aralkyl. More preferably, each of P^1 and P^2 is benzyl.

Additionally, the P^1 and/or P^2 protecting groups can form a heterocyclic ring with the nitrogen to which they are attached, for example, 1,2-bis(methylene)benzene, phthalimidyl, succinimidyl, maleimidyl and the like and where these heterocyclic groups can further include adjoining aryl and cycloalkyl rings. In addition, the heterocyclic groups can be mono-, di- or tri-substituted, e.g., nitrophthalimidyl. The term silyl refers to a silicon atom optionally substituted by one or more alkyl, aryl and aralkyl groups.

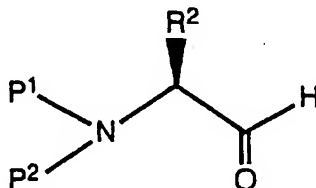
Suitable silyl protecting groups include, but are not limited to, trimethylsilyl, triethylsilyl, tri-isopropylsilyl, tert-butyldimethylsilyl, dimethylphenylsilyl, 1,2-bis(dimethylsilyl)benzene, 1,2-bis(dimethylsilyl)ethane and diphenylmethylsilyl. Silylation of the amine functions to provide mono- or bis-disilylamine can provide derivatives of the aminoalcohol, amino acid, amino acid esters and amino acid amide. In the case of amino acids, amino acid esters and amino acid amides, reduction of the carbonyl function provides the required mono- or bis-silyl aminoalcohol. Silylation of the aminoalcohol can lead to the N,N,O-tri-silyl derivative. Removal of the silyl function from the silyl ether function is readily accomplished by treatment with, for example, a metal hydroxide or ammonium fluoride reagent, either as a discrete reaction step or in situ during the preparation of the amino aldehyde reagent. Suitable silylating agents are, for example, trimethylsilyl chloride, tert-butyldimethylsilyl chloride, phenyldimethylsilyl chloride, diphenylmethylsilyl chloride or their combination products with imidazole or DMF. Methods for silylation of amines and removal of silyl protecting groups are well known to those skilled in the art. Methods of preparation of these amine derivatives from corresponding amino acids, amino acid amides or amino acid esters are also well known to those skilled in the art of organic chemistry including amino acid/amino acid ester or aminoalcohol chemistry.

30

The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78°C in a suitable solvent such as toluene. Preferred reducing agents include lithium aluminium hydride, lithium borohydride, sodium borohydride, borane, lithium tri-ter-

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butoxyaluminum hydride, borane/THF complex. Most preferably, the reducing agent is diisobutylaluminum hydride (DiBAL-H) in toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



wherein P¹, P² and R² are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

Acceptable oxidizing reagents include, for example, sulfur trioxide-pyridine complex and DMSO, oxalyl chloride and DMSO, acetyl chloride or anhydride and DMSO, trifluoroacetyl chloride or anhydride and DMSO, methanesulfonyl chloride and DMSO or tetrahydro thiophene-S-oxide, toluenesulfonyl bromide and DMSO, trifluoromethanesulfonyl anhydride (triflic anhydride) and DMSO, phosphorus pentachloride and DMSO, dimethylphosphoryl chloride and DMSO and isobutyl chloroformate and DMSO. The oxidation conditions reported by Reetz et al [Angew Chem., 99, p. 1186, (1987)], Angew Chem. Int. Ed. Engl., 26, p. 1141, 1987) employed oxalyl chloride and DMSO at -78°C.

The preferred oxidation method described in this invention is sulfur trioxide pyridine complex, triethylamine and DMSO at room temperature. This system provides excellent yields of the desired chiral protected amino aldehyde usable without the need for purification i.e., the need to purify kilograms of intermediates by

chromatography is eliminated and large scale operations are made less hazardous. Reaction at room temperature also eliminated the need for the use of low temperature reactor which makes the process more suitable for commercial production.

The reaction may be carried out under an inert atmosphere such as nitrogen or argon, or normal or dry air, under atmospheric pressure or in a sealed reaction vessel under positive pressure. Preferred is a nitrogen atmosphere. Alternative amine bases include, for example, tri-butyl amine, tri-isopropyl amine, N-methylpiperidine, N-methyl morpholine, azabicyclononane, diisopropylethylamine, 2,2,6,6-tetramethylpiperidine, N,N-dimethylaminopyridine, or mixtures of these bases. Triethylamine is a preferred base. Alternatives to pure DMSO as solvent include mixtures of DMSO with non-protic or halogenated solvents such as tetrahydrofuran, ethyl acetate, toluene, xylene, dichloromethane, ethylene dichloride and the like. Dipolar aprotic co-solvents include acetonitrile, dimethylformamide, dimethylacetamide, acetamide, tetramethyl urea and its cyclic analog, N-methylpyrrolidone, sulfolane and the like. Rather than N,N-dibenzylphenylalaninol as the aldehyde precursor, the phenylalaninol derivatives discussed above can be used to provide the corresponding N-monosubstituted [either P^1 or $P^2 = H$] or N,N-disubstituted aldehyde.

In addition, hydride reduction of an amide or ester derivative of the corresponding benzyl (or other suitable protecting group) nitrogen protected phenylalanine, substituted phenylalanine or cycloalkyl analog of phenylalanine derivative can be carried out to provide the aldehydes. Hydride transfer is an additional method of aldehyde synthesis under conditions where aldehyde condensations are avoided, cf, Oppenauer Oxidation.

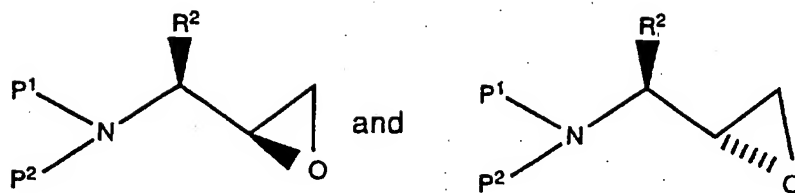
The aldehydes of this process can also be prepared by methods of reducing protected phenylalanine and phenylalanine analogs or their amide or ester derivatives by, e.g., sodium amalgam with HCl in ethanol or lithium or sodium or potassium or calcium in ammonia. The reaction temperature may be from about -20°C to about 45°C, and preferably from about 5°C to about 25°C. Two additional methods of obtaining the nitrogen protected aldehyde include oxidation of the corresponding alcohol with bleach in the presence of a catalytic amount of 2,2,6,6-tetramethyl-1-pyridyloxy free radical. In a second method, oxidation of the alcohol to the aldehyde is accomplished by a catalytic amount of tetrapropylammonium perruthenate in the presence of N-methylmorpholine-N-oxide.

Alternatively, an acid chloride derivative of a protected phenylalanine or phenylalanine derivative as disclosed above can be reduced with hydrogen and a catalyst such as Pd on barium carbonate or barium sulphate, with or without an additional catalyst moderating agent such as sulfur or a thiol (Rosenmund Reduction).

25

The aldehyde resulting from the Swern oxidation is then reacted with a halomethylolithium reagent, which reagent is generated in situ by reacting an alkylolithium or arylolithium compound with a dihalomethane represented by the formula $X^1CH_2X^2$ wherein X^1 and X^2 independently represent I, Br or Cl. For example, a solution of the aldehyde and chloriodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:

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The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. A D-amino acid can be utilized in place of the L-amino acid in order to prepare compounds having an (S) stereochemistry at the carbon bonded to R².

- 10 The addition of chloromethylithium or bromomethylithium to a chiral amino aldehyde is highly diastereoselective. Preferably, the chloromethylithium or bromomethylithium is generated in-situ from the reaction of the dihalomethane and n-butyllithium.
- 15 Acceptable methyleneating halomethanes include chloriodomethane, bromochloromethane, dibromomethane, diiodomethane, bromofluoromethane and the like. The sulfonate ester of the addition product of, for example, hydrogen bromide to formaldehyde is also a methyleneating agent. Tetrahydrofuran is the preferred solvent, however
- 20 alternative solvents such as toluene, dimethoxyethane, ethylene dichloride, methylene chloride can be used as pure solvents or as a mixture. Dipolar aprotic solvents such as acetonitrile, DMF, N-methylpyrrolidone are useful as solvents or as part of a solvent mixture. The
- 25 reaction can be carried out under an inert atmosphere such as nitrogen or argon. For n-butyl lithium can be substituted other organometallic reagents reagents such as methylithium, tert-butyl lithium, sec-butyl lithium, phenyllithium, phenyl sodium and the like. The reaction
- 30 can be carried out at temperatures of between about -80°C to 0°C but preferably between about -80°C to -20°C. The most preferred reaction temperatures are between -40°C to -15°C. Reagents can be added singly but multiple

additions are preferred in certain conditions. The preferred pressure of the reaction is atmospheric however a positive pressure is valuable under certain conditions such as a high humidity environment.

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Alternative methods of conversion to the epoxides of this invention include substitution of other charged methylenation precursor species followed by their treatment with base to form the analogous anion.

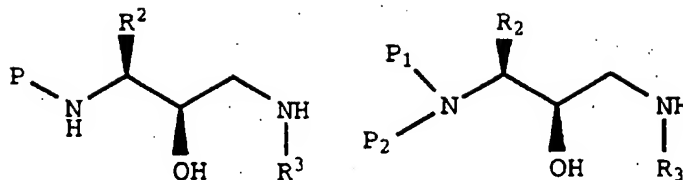
10 Examples of these species include trimethylsulfoxonium tosylate or triflate, tetramethylammonium halide, methyldiphenylsulfoxonium halide wherein halide is chloride, bromide or iodide.

15 The conversion of the aldehydes of this invention into their epoxide derivative can also be carried out in multiple steps. For example, the addition of the anion of thioanisole prepared from, for example, a butyl or aryl lithium reagent, to the protected aminoaldehyde, 20 oxidation of the resulting protected aminosulfide alcohol with well known oxidizing agents such as hydrogen peroxide, tert-butyl hypochlorite, bleach or sodium periodate to give a sulfoxide. Alkylation of the sulfoxide with, for example, methyl iodide or bromide, 25 methyl tosylate, methyl mesylate, methyl triflate, ethyl bromide, isopropyl bromide, benzyl chloride or the like, in the presence of an organic or inorganic base. Alternatively, the protected aminosulfide alcohol can be alkylated with, for example, the alkylating agents above, 30 to provide sulfonium salts that are subsequently converted into the subject epoxides with tert-amine or mineral bases.

The desired epoxides formed, using most preferred 35 conditions, diastereoselectively in ratio amounts of at least about an 85:15 ratio (S:R). The product can be purified by chromatography to give the diastereomerically

and enantiomerically pure product but it is more conveniently used directly without purification to prepare retroviral protease inhibitors. The foregoing process is applicable to mixtures of optical isomers as well as resolved compounds. If a particular optical isomer is desired, it can be selected by the choice of starting material, e.g., L-phenylalanine, D-phenylalanine, L-phenylalaninol, D-phenylalaninol, D-hexahydrophenylalaninol and the like, or resolution can occur at intermediate or final steps. Chiral auxiliaries such as one or two equivalents of camphor sulfonic acid, citric acid, camphoric acid, 2-methoxyphenylacetic acid and the like can be used to form salts, esters or amides of the compounds of this invention. These compounds or derivatives can be crystallized or separated chromatographically using either a chiral or achiral column as is well known to those skilled in the art.

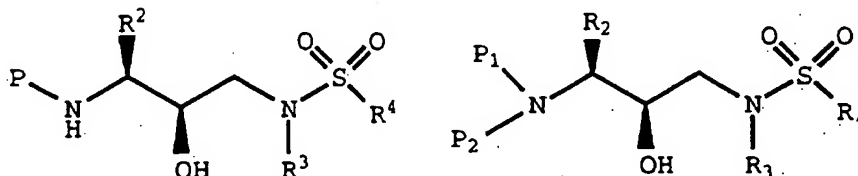
The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an excess of, a desired amine of the formula R^3NH_2 , wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures thereof. A preferred solvent is isopropanol. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:



wherein P, P¹, P², R² and R³ are as described above.

Alternatively, a haloalcohol can be utilized in place of the amino epoxide.

The amino alcohol defined above is then reacted in a suitable solvent with the sulfonyl chloride R⁴SO₂Cl, the sulfonyl bromide R⁴SO₂Br or the corresponding sulfonyl anhydride, preferably in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran and the like. Suitable acid scavengers include triethylamine, pyridine and the like. The resulting sulfonamide derivative can be represented, depending on the epoxide utilized by the formulas

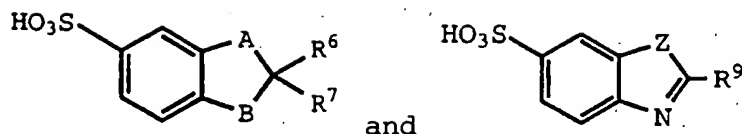


wherein P, P¹, P², R², R³ and R⁴ are as defined above. These intermediates are useful for preparing inhibitor compounds of the present invention.

The sulfonyl halides of the formula R⁴SO₂X can be prepared by the reaction of a suitable aryl, heteroaryl and benzo fused heterocyclo Grignard or lithium reagents with sulfonyl chloride, or sulfur dioxide followed by oxidation with a halogen, preferably chlorine. Aryl, heteroaryl and benzo fused heterocyclo Grignard or lithium reagents can be prepared from their corresponding halide (such as chloro or bromo) compounds which are

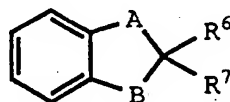
commercially available or readily prepared from commercially available starting materials using known methods in the art. Also, thiols may be oxidized to sulfonyl chlorides using chlorine in the presence of water under carefully controlled conditions. Additionally, sulfonic acids, such as arylsulfonic acids, may be converted to sulfonyl halides using reagents such as PCl_5 , SOCl_2 , ClC(O)C(O)Cl and the like, and also to anhydrides using suitable dehydrating reagents. The sulfonic acids may in turn be prepared using procedures well known in the art. Some sulfonic acids are commercially available. In place of the sulfonyl halides, sulfinyl halides (R^4SOX) or sulfenyl halides (R^4SX) can be utilized to prepare compounds wherein the $-\text{SO}_2-$ moiety is replaced by an $-\text{SO}-$ or $-\text{S}-$ moiety, respectively. Arylsulfonic acids, benzo fused heterocyclo sulfonic acids or heteroaryl sulfonic acids can be prepared by sulfonation of the aromatic ring by well known methods in the art, such as by reaction with sulfuric acid, SO_3 , SO_3 complexes, such as $\text{DMF}(\text{SO}_3)$, pyridine(SO_3), N,N -dimethylacetamide(SO_3), and the like. Preferably, arylsulfonyl halides are prepared from aromatic compounds by reaction with $\text{DMF}(\text{SO}_3)$ and SOCl_2 or ClC(O)C(O)Cl . The reactions may be performed stepwise or in a single pot.

Arylsulfonic acids, benzo fused heterocyclo sulfonic acids, heteroaryl sulfonic acids, arylmercaptans, benzo fused heterocyclo mercaptans, heteroarylmercaptans, arylhalides, benzo fused heterocyclo halides, heteroarylhalides, and the like are commercially available or can be readily prepared from starting materials commercially available using standard methods well known in the art. For example, a number of sulfonic acids ($\text{R}^4\text{SO}_3\text{H}$) represented by the formulas

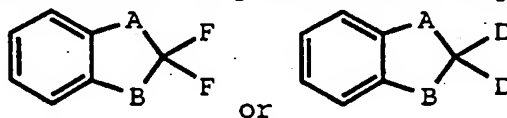


and

wherein A, B, Z, R⁶, R⁷ and R⁹ are as defined above, have been prepared from 1,2-benzenedithiol, 2-mercaptophenol, 1,2-benzenediol, 2-aminobenzothiazole, benzothiazole, 2-aminobenzimidazole, benzimidazole, and the like, which are commercially available, by Carter, US Patent 4,595,407; Ehrenfreund et al., US Patent 4,634,465; Yoder et al., J. Heterocycl. Chem. 4:166-167 (1967); Cole et al., Aust. J. Chem. 33:675-680 (1980); Cabiddu et al., Synthesis 797-798 (1976); Ncube et al., Tet. Letters 2345-2348 (1978); Ncube et al., Tet. Letters 255-256 (1977); Ansink & Cerfontain, Rec. Trav. Chim. Pays-Bas 108:395-403 (1989); and Kajihara & Tsuchiya, EP 638564 A1, each of which are incorporated herein by reference in their entirety. For example, 1,2-benzenedithiol, 2-mercaptophenol or 1,2-benzenediol can be reacted with R⁶R⁷C(L')₂, where L' is as defined below, preferably, Br or I, in the presence of a base, such as hydroxide, or R⁶R⁷C=O in the presence of acid, such as toluenesulfonic acid, or P₂O₅, to prepare the substituted benzo fused heterocycle of formula



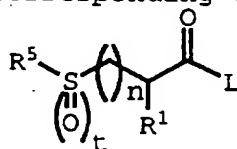
which can then be sulfonylated to the sulfonic acid above. For example, CF₂Br₂ or CD₂Br₂ can be reacted with 1,2-benzenedithiol, 2-mercaptophenol or 1,2-benzenediol in the presence of base to produce the compounds



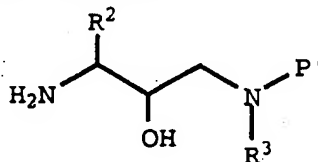
respectively, wherein A and B are O or S and D is a deuterium atom. Also, when A and/or B represent S, the sulfur can be oxidized using the methods described below to the sulfone or sulfoxide derivatives.

Following preparation of the sulfonamide derivative, the amino protecting group P or P¹ and P² amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative.

Following neutralization of the salt, the amine is then coupled to the sulfone/sulfoxidealkanoyl compound or an optical isomer thereof (such as where the group -CH(R¹)- is R or S), corresponding to the formula

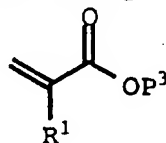


wherein n, t and R⁵ are as defined above, and L is leaving group such as halide, anhydride, active ester, and the like. Alternatively, the sulfone/sulfoxide alkanoyl compound or an optical isomer thereof can be coupled to the protected amine

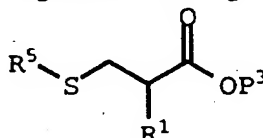


followed by deprotection and coupling to R⁴SO₂X, where X is Cl or Br and P', R², R³ and R⁴ is as defined above.

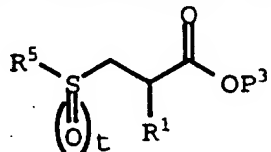
Such sulfone/sulfoxidealkanoyl compounds where n is 1 can be prepared by reacting a mercaptan of the formula R^5SH with a substituted methacrylate of the formula



5 by way of a Michael Addition. Such substituted methacrylates are commercially available or readily prepared from commercially available starting materials using standard methods well known in the art. The Michael Addition is conducted in a suitable solvent and in the
10 presence of a suitable base, to produce the corresponding thioether derivative represented by the formula



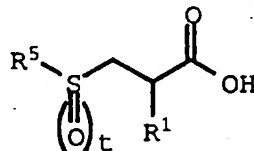
wherein P^3 , R^1 and R^5 are as defined above. Suitable solvents in which the Michael Addition can be conducted
15 include alcohols such as, for example, methanol, ethanol, butanol and the like, as well as ethers, e.g., THF, and acetonitrile, DMF, DMSO, and the like, including mixtures thereof. Suitable bases include Group I metal alkoxides such as, for example sodium methoxide, sodium ethoxide,
20 sodium butoxide and the like as well as Group I metal hydrides, such as sodium hydride, including mixtures thereof. The thioether derivative is converted into the corresponding sulfone or sulfoxide of the formula



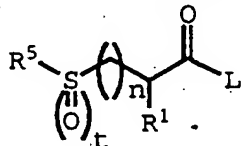
25 by oxidizing the thioether derivative with a suitable oxidation agent in a suitable solvent. Suitable oxidation agents include, for example, hydrogen peroxide, sodium meta-perborate, oxone (potassium peroxy monosulfate), meta-chloroperoxybenzoic acid, periodic
30 acid and the like, including mixtures thereof. Suitable

solvents include acetic acid (for sodium ~~meta~~-perborate) and, for other peracids, ethers such as THF and dioxane, and acetonitrile, DMF and the like, including mixtures thereof.

- 5 The sulfone/sulfoxide is then converted into the corresponding free acid of the formula

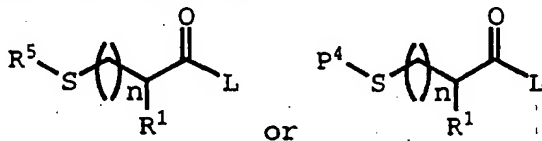


- utilizing a suitable base, e.g., lithium hydroxide, sodium hydroxide, and the like, including mixtures thereof, in a suitable solvent, such as, for example, THF, acetonitrile, DMF, DMSO, methylene chloride and the like, including mixtures thereof. The free acid can then be converted into the sulfone/sulfoxidealkanoyl compound

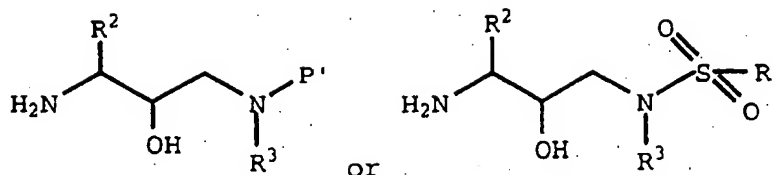


- 15 wherein n, t and R⁵ are as defined above, and L is leaving group such as halide, anhydride, active ester, and the like. Alternatively, the free acid can be resolved into its optical isomers (such as where the group -CH(R¹)- is R or S) using well known methods in the art, such as by forming diastereomeric salts or esters and crystallizing or chromatographing, and then converted into the sulfone/sulfoxidealkanoyl compound.

- 25 Alternatively, the thioether or corresponding protected thiol of formulas

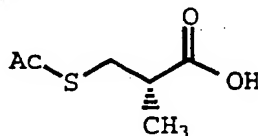


respectively, where n, L, R¹ and R⁵ are as defined above, can be coupled to one of the amines

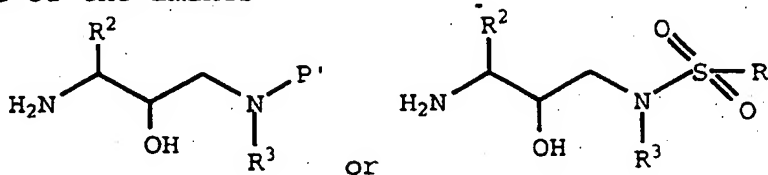


followed by conversion to the protease inhibitors of the present invention. P^4 is a sulfur protecting group, such as acetyl, benzoyl and the like. The acetyl and benzoyl groups can be removed by treatment with an inorganic base or an amine, preferably ammonia, in an appropriate solvent such as methanol, ethanol, isopropanol, toluene or tetrahydrofuran. The preferred solvent is methanol.

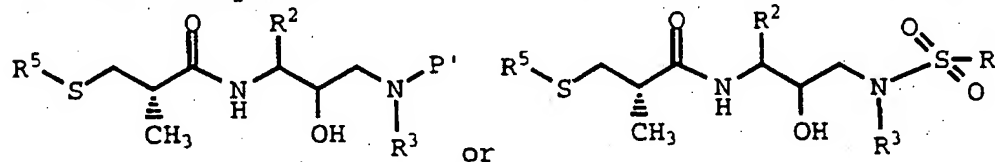
For example, one can couple the commercially available acid



to one of the amines

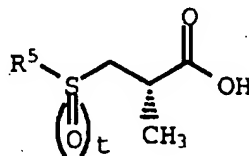


deacetylate the sulfur group, such as by hydrolysis with a suitable base, such as hydroxide, or an amine, such as ammonia, and then react the resulting thiol with R^5L' agent, wherein R^5 and L' are as defined above, to afford compounds with one of the following structures



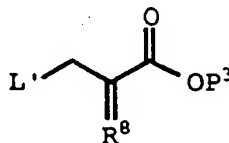
or specific diastereomeric isomers thereof. The sulfur can then be oxidized to the corresponding sulfone or sulfoxide using suitable oxidizing agents, as described above, to afford the desired intermediate followed by further reactions to prepare the sulfonamide inhibitor, or directly to the sulfonamide inhibitor. Alternatively,

the acid or the P³ protected acid can be deacetylated, reacted with R⁵L' agent, deprotected and oxidized to the corresponding sulfone or sulfoxide using suitable oxidizing agents, as described above to afford the compound of formula



wherein t and R⁵ are as defined above. This sulfone/sulfoxide carboxylic acid can then be coupled to the amine intermediate described above followed by further reaction to prepare the sulfonamide inhibitor, or to the sulfonamide amine compound to produce the sulfonamide inhibitor directly. The L' group of the R⁵L' agent is a leaving group such as a halide (chloride, bromide, iodide), mesylate, tosylate or triflate. The reaction of the mercaptan with R⁵L' is performed in the presence of a suitable base, such as triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) and the like, in a suitable solvent such as toluene, tetrahydrofuran, methylene chloride or dimethylacetamide. The preferred base is DBU and the preferred solvent is toluene or dimethylacetamide. Where R⁵ is a methyl group, R⁵L' can be methyl chloride, methyl bromide, methyl iodide, or dimethyl sulfate, and preferably methyl iodide.

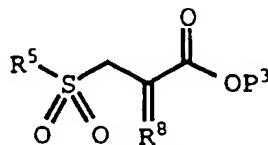
Alternatively, a substituted methacrylate of the formula



wherein L' represents a leaving group as previously defined, P³ is as defined above and R⁸ represents radicals which upon reduction of the double bond produce radicals of R¹, is reacted with R⁵SM followed by oxidation, as described above, or a suitable sulfonating

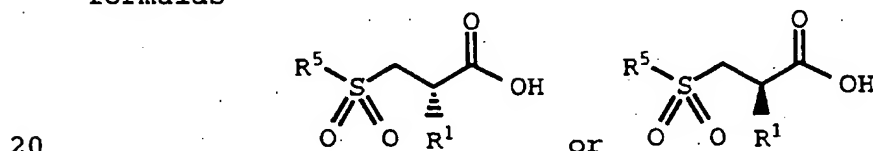
agent, such as, for example, a sulfinic acid represented by the formula R^5SO_2M , wherein R^5 is as defined above and M represents a metal adapted to form a salt of the acid, e.g., sodium, to produce the corresponding sulfone

5 represented by the formula



wherein P^3 , R^5 and R^8 are as defined above. The sulfone is then deprotected to form the corresponding carboxylic acid. For example, when P^3 is a tertiary-butyl group, it can be removed by treatment with an acid, such as hydrochloric acid or trifluoroacetic acid. The preferred method is using 4N hydrochloric acid in dioxane.

The resulting carboxylic acid is then asymmetrically hydrogenated utilizing an asymmetric hydrogenation catalyst such as, for example, a ruthenium-BINAP complex, to produce the reduced product, substantially enriched in the more desired isomer, represented by one of the formulas



wherein R^1 and R^5 are as defined above. Where the more active isomer has the R-stereochemistry, a Ru(R-BINAP) asymmetric hydrogenation catalyst can be utilized.

Conversely, where the more active isomer has the S-

25 stereochemistry, a Ru(S-BINAP) catalyst can be utilized.

Where both isomers are active, or where it is desired to have a mixture of the two diastereomers, a hydrogenation catalyst such as platinum or palladium on carbon can be utilized to reduce the above compound. The reduced

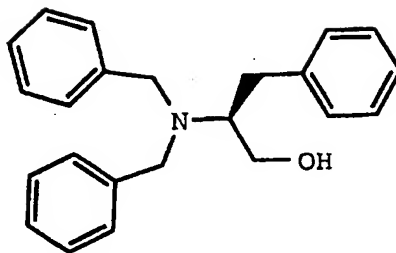
30 compound is then coupled to an amine as described above.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily prepared from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received without purification. All proton and carbon NMR spectra were obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

The following Examples illustrate the preparation of inhibitor compounds of the present invention and intermediates useful in preparing the inhibitor compounds of the present invention.

EXAMPLE 15 Preparation of 2S-[Bis(phenylmethyl)amino]benzenepropanol

METHOD 1: 2S-[Bis(phenylmethyl)amino]benzenepropanol
from the DIBAL Reduction of N,N-bis(phenylmethyl)-L-
Phenylalanine phenylmethyl ester

10

Step 1:

A solution of L-phenylalanine (50.0 g, 0.302 mol),
sodium hydroxide (24.2 g, 0.605 mol) and potassium
carbonate (83.6 g, 0.605 mol) in water (500 mL) was
15 heated to 97°C. Benzyl bromide (108.5 mL, 0.605 mol) was
then slowly added (addition time - 25 min). The mixture
was stirred at 97°C for 30 minutes under a nitrogen
atmosphere. The solution was cooled to room temperature
and extracted with toluene (2 x 250 mL). The combined
20 organic layers were washed with water and brine, dried
over magnesium sulfate, filtered and concentrated to an
oil. The identity of the product was confirmed as
follows. Analytical TLC (10% ethyl acetate/hexane,
silica gel) showed major component at R_f value = 0.32 to
25 be the desired tribenzylated compound, N,N-bis(phenyl
methyl)-L-phenylalanine phenylmethyl ester. This
compound can be purified by column chromatography (silica
gel, 15% ethyl acetate/hexane). Usually the product is
pure enough to be used directly in the next step without
30 further purification. ¹H NMR spectrum was in agreement
with published literature. ¹H NMR (CDCl₃) δ, 3.00 and
3.14 (ABX-system, 2H, J_{AB}=14.1 Hz, J_{AX}=7.3 Hz and J_{BX}=

5.9 Hz), 3.54 and 3.92 (AB-System, 4 H, $J_{AB}=13.9$ Hz), 3.71 (t, 1H, $J=7.6$ Hz), 5.11 and 5.23 (AB-System, 2H, $J_{AB}=12.3$ Hz), and 7.18 (m, 20 H). EIMS: m/z 434 (M-1).

5 Step 2:

The benzylated phenylalanine phenylmethyl ester (0.302 mol) from the previous reaction was dissolved in toluene (750 mL) and cooled to -55°C . A 1.5 M solution of DIBAL in toluene (443.9 mL, 0.666 mol) was added at a rate to maintain the temperature between -55 to -50°C (addition time - 1 hr). The mixture was stirred for 20 minutes under a nitrogen atmosphere and then quenched at -55°C by the slow addition of methanol (37 ml). The cold solution was then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid (approx. 138 g) was filtered off and washed with toluene. The solid material was suspended in a mixture of toluene (400 mL) and water (100 ml). The mixture was cooled to 5°C and treated with 2.5 N NaOH (186 mL) and then stirred at room temperature until solid dissolved. The toluene layer was separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 mL (89 g). Ethyl acetate (25 mL) and hexane (25 mL) were added to the residue upon which the desired alcohol product began to crystallize. After 30 min, an additional 50 mL hexane were added to promote further crystallization. The solid was filtered off and washed with 50 mL hexane to give 34.9 g of first crop product. A second crop of product (5.6 g) was isolated by refiltering the mother liquor. The two crops were combined and recrystallized from ethyl acetate (20 mL) and hexane (30 mL) to give 40 g of β S-2-[Bis(phenylmethyl)aminol]benzenepropanol, 40% yield from L-phenylalanine. An additional 7 g (7%) of product can be obtained from recrystallization of the concentrated mother liquor. TLC of product $R_f = 0.23$ (10% ethyl acetate/hexane, silica gel); ^1H NMR (CDCl_3) δ 2.44 (m,

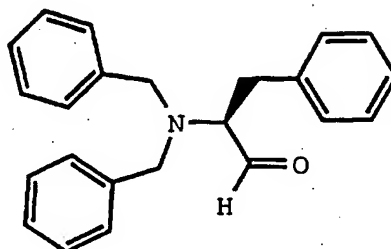
1H,), 3.09 (m, 2H), 3.33 (m, 1H), 3.48 and 3.92 (AB-System, 4H, J_{AB} = 13.3 Hz), 3.52 (m, 1H) and 7.23 (m, 15H); [α]_D²⁵ +42.4 (c 1.45, CH₂Cl₂); DSC 77.67°C; Anal. Calcd. for C₂₃H₂₅ON: C, 83.34; H, 7.60; N, 4.23. Found: 5 C, 83.43; H, 7.59; N, 4.22. HPLC on chiral stationary phase: Cyclobond I SP column (250 x 4.6 mm I.D.), mobile phase: methanol/triethyl ammonium acetate buffer pH 4.2 (58:42, v/v), flow-rate of 0.5 ml/min, detection with 10 detector at 230nm and a temperature of 0°C. Retention time: 11.25 min., retention time of the desired product enantiomer: 12.5 min.

METHOD 2: Preparation of β S-2-[Bis(phenylmethyl)amino] benzene-propanol from the N,N-Dibenzylation of 15 L-Phenylalaninol

L-phenylalaninol (176.6 g, 1.168 mol) was added to a stirred solution of potassium carbonate (484.6 g, 3.506 mol) in 710 mL of water. The mixture was heated to 65°C 20 under a nitrogen atmosphere. A solution of benzyl bromide (400 g, 2.339 mol) in 3A ethanol (305 mL) was added at a rate that maintained the temperature between 60-68°C. The biphasic solution was stirred at 65°C for 55 min and then allowed to cool to 10°C with vigorous 25 stirring. The oily product solidified into small granules. The product was diluted with 2.0 L of tap water and stirred for 5 minutes to dissolve the inorganic by products. The product was isolated by filtration under reduced pressure and washed with water until the pH is 7. 30 The crude product obtained was air dried overnight to give a semi-dry solid (407 g) which was recrystallized from 1.1 L of ethyl acetate/heptane (1:10 by volume). The product was isolated by filtration (at -8°C), washed with 1.6 L of cold (-10°C) ethyl acetate/heptane 35 (1:10 by volume) and air-dried to give 339 g (88% yield) of β S-2-[Bis(phenylmethyl)amino]benzene-propanol, Mp = 71.5-73.0°C. More product can be obtained from the

mother liquor if necessary. The other analytical characterization was identical to compound prepared as described in Method 1.

5

EXAMPLE 2Preparation of 2S-[Bis(phenylmethyl)amino]benzene propanaldehyde

10

METHOD 1:

2S-[Bis(phenylmethyl)amino]benzene-propanol (200 g, 0.604 mol) was dissolved in triethylamine (300 mL, 2.15 mol). The mixture was cooled to -12°C and a solution of sulfur trioxide/pyridine complex (380 g, 2.39 mol) in DMSO (1.6 L) was added at a rate to maintain the temperature between 8-17°C (addition time - 1.0 h). The solution was stirred at ambient temperature under a nitrogen atmosphere for 1.5 hour at which time the reaction was complete by TLC analysis (33% ethyl acetate/hexane, silica gel). The reaction mixture was cooled with ice water and quenched with 1.6 L of cold water (10-15°C) over 45 minutes. The resultant solution was extracted with ethyl acetate (2.0 L), washed with 5% citric acid (2.0 L), and brine (2.2 L), dried over MgSO₄ (280 g) and filtered. The solvent was removed on a rotary evaporator at 35-40°C and then dried under vacuum to give 198.8 g of 2S-[Bis-(phenylmethyl)amino]benzene propanaldehyde as a pale yellow oil (99.9%). The crude product obtained was pure enough to be used directly in the next step without purification. The analytical data of the compound were consistent with the published

30

literature. $[\alpha]_{D25} = -92.9^\circ$ (c 1.87, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ , 2.94 and 3.15 (ABX-System, 2H, $J_{AB} = 13.9$ Hz, $J_{AX} = 7.3$ Hz and $J_{BX} = 6.2$ Hz), 3.56 (t, 1H, 7.1 Hz), 3.69 and 3.82 (AB-System, 4H, $J_{AB} = 13.7$ Hz), 7.25 (m, 15 H) and 9.72 (s, 1H); HRMS Calcd for (M+1) $\text{C}_{23}\text{H}_{24}\text{NO}$ 330.450, found: 330.1836. Anal. Calcd. for $\text{C}_{23}\text{H}_{23}\text{ON}$: C, 83.86; H, 7.04; N, 4.25. Found: C, 83.64; H, 7.42; N, 4.19. HPLC on chiral stationary phase: (S,S) Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of the desired S-isomer: 8.75 min., retention time of the R-enantiomer 10.62 min.

15 METHOD 2:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) was cooled to -74°C . A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) was then slowly added at a rate to maintain the temperature at -74°C (addition time ~1.25 hr). The mixture was stirred for 5 min. followed by addition of a solution of $\beta\text{S-2-[bis(phenylmethyl)amino]benzene-propanol}$ (0.074 mol) in 100 ml of dichloromethane (addition time ~20 min., temp. -75°C to -68°C). The solution was stirred at -78°C for 35 minutes under a nitrogen atmosphere. Triethylamine (41.2 ml, 0.295 mol) was then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture was stirred for 30 min. and then water (225 ml) was added. The dichloromethane layer was separated from the aqueous phase and washed with water, brine, dried over magnesium sulfate, filtered and concentrated. The residue was diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate was concentrated to give $\alpha\text{S-[bis(phenylmethyl)amino]benzenepropanaldehyde}$. The aldehyde was carried on to the next step without purification.

METHOD 3:

To a mixture of 1.0 g (3.0 mmol) of β S-2-[bis(phenylmethyl)amino]benzenepropanol 0.531 g (4.53 mmol) of N-methyl morpholine, 2.27 g of molecular sieves (4A) and 9.1 mL of acetonitrile was added 53 mg (0.15 mmol) of tetrapropylammonium perruthenate (TPAP). The mixture was stirred for 40 minutes at room temperature and concentrated under reduced pressure. The residue was suspended in 15 mL of ethyl acetate, filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a product containing approximately 50% of α S-2-[bis(phenylmethyl)amino]benzene propanaldehyde as a pale yellow oil.

METHOD 4:

To a solution of 1.0 g (3.02 mmol) of β S-2-[bis(phenylmethyl)amino]benzenepropanol in 9.0 mL of toluene was added 4.69 mg (0.03 mmol) of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), 0.32 g (3.11 mmol) of sodium bromide, 9.0 mL of ethyl acetate and 1.5 mL of water. The mixture was cooled to 0°C and an aqueous solution of 2.87 mL of 5% household bleach containing 0.735 g (8.75 mmol) of sodium bicarbonate and 8.53 mL of water was added slowly over 25 minutes. The mixture was stirred at 0°C for 60 minutes. Two more additions (1.44 mL each) of bleach was added followed by stirring for 10 minutes. The two phase mixture was allowed to separate. The aqueous layer was extracted twice with 20 mL of ethyl acetate. The combined organic layer was washed with 4.0 mL of a solution containing 25 mg of potassium iodide and water (4.0 mL), 20 mL of 10% aqueous sodium thiosulfate solution and then brine solution. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 1.34 g of crude oil containing a small amount of the desired

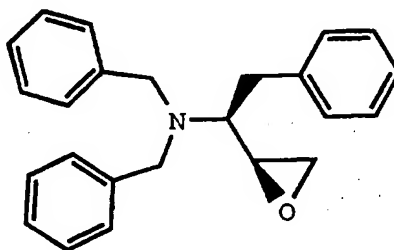
product aldehyde, α S-[bis(phenylmethyl)amino]benzenepropanaldehyde.

METHOD 5:

- 5 Following the same procedures as described in Method 1 of this Example except 3.0 equivalents of sulfur trioxide pyridine complex was used and α S-[bis(phenylmethyl)amino]benzenepropanaldehyde was isolated in comparable yields.

10

EXAMPLE 3



- 15 Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

METHOD 1:

- 20 A solution of α S-[Bis(phenylmethyl)amino]benzenepropanaldehyde (191.7 g, 0.58 mol) and chloriodomethane (56.4 mL, 0.77 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyl lithium in hexane (1.6 M, 365 mL, 0.58 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional chloriodomethane (17 mL) was added, followed by n-butyl lithium (110 mL) at < -25°C. After addition the mixture
- 25
- 30

was stirred at -30 to -35°C for 10 minutes. This was repeated once. (2) Additional chloriodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyl lithium (55 mL, 0.088 mol) at <-25°C. After addition the mixture was

5 stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional chloriodomethane (8.5 mL, 0.11 mol) was added, followed by n-butyl lithium (37 mL, 0.059 mol) at <-25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was

10 repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium

15 chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl

20 acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo

25 (0.8 bar) for 1 h to give 222.8 g of crude material. (The crude product weight was >100%. Due to the relative instability of the product on silica gel, the crude product is usually used directly in the next step without purification). The diastereomeric ratio of the crude

30 mixture was determined by proton NMR: (2S)/(2R): 86:14. The minor and major epoxide diastereomers were characterized in this mixture by tlc analysis (silica gel, 10% ethyl acetate/hexane), $R_f = 0.29$ & 0.32 , respectively. An analytical sample of each of the

35 diastereomers was obtained by purification on silica-gel chromatography (3% ethyl acetate/hexane) and characterized as follows:

N,N, α S-Tris(phenylmethyl)-2S-oxiranemethanamine

¹H NMR (400 MHz, CDCl₃) δ 2.49 and 2.51 (AB-System, 1H, J_{AB} = 2.82), 2.76 and 2.77 (AB-System, 1H, J_{AB} = 4.03), 2.83 (m, 2H), 2.99 & 3.03 (AB-System, 1H, J_{AB} = 10.1 Hz), 3.15 (m, 1H), 3.73 & 3.84 (AB-System, 4H, J_{AB} = 14.00), 7.21 (m, 15H); ¹³C NMR (400 MHz, CDCl₃) δ 139.55, 129.45, 128.42, 128.14, 128.09, 126.84, 125.97, 60.32, 54.23, 52.13, 45.99, 33.76; HRMS Calcd for C₂₄H₂₆NO (M+1) 344.477, found 344.2003.

N,N, α S-Tris(phenylmethyl)-2R-oxiranemethanamine

¹H NMR (300 MHz, CDCl₃) δ 2.20 (m, 1H), 2.59 (m, 1H), 2.75 (m, 2H), 2.97 (m, 1H), 3.14 (m, 1H), 3.85 (AB-System, 4H), 7.25 (m, 15H). HPLC on chiral stationary phase: Pirkle-Whelk-O 1 column (250 x 4.6 mm I.D.), mobile phase: hexane/isopropanol (99.5:0.5, v/v), flow-rate: 1.5 ml/min, detection with UV detector at 210nm. Retention time of (8): 9.38 min., retention time of enantiomer of (4): 13.75 min.

METHOD 2:

A solution of the crude aldehyde 0.074 mol and chloriodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) was cooled to -78°C, under a nitrogen atmosphere. A 1.6 M solution of n-butyl lithium in hexane (25 ml, 0.040 mol) was then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloriodomethane (1.6 ml, 0.022 mol) was added again, followed by n-butyl lithium (23 ml, 0.037 mol), keeping the temperature at -75°C. The mixture was stirred for 15 min. Each of the reagents, chloriodomethane (0.70 ml, 0.010 mol) and n-butyl lithium (5 ml, 0.008 mol) were added 4 more times over 45 min. at -75°C. The cooling

bath was then removed and the solution warmed to 22°C over 1.5 hr. The mixture was poured into 300 ml of saturated aq. ammonium chloride solution. The tetrahydrofuran layer was separated. The aqueous phase
5 was extracted with ethyl acetate (1 x 300 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer
10 can be purified by recrystallization at a subsequent step. The product could also be purified by chromatography.

METHOD 3:

15 A solution of α S-[Bis(phenylmethyl)amino]benzene-propanaldehyde (178.84 g, 0.54 mol) and bromochloromethane (46 mL, 0.71 mol) in tetrahydrofuran (1.8 L) was cooled to -30 to -35°C (colder temperature such as -70°C also worked well but warmer temperatures are more readily
20 achieved in large scale operations) in a stainless steel reactor under a nitrogen atmosphere. A solution of n-butyl lithium in hexane (1.6 M, 340 mL, 0.54 mol) was then added at a rate that maintained the temperature below -25°C. After addition the mixture was stirred at
25 -30 to -35°C for 10 minutes. More additions of reagents were carried out in the following manner: (1) additional bromochloromethane (14 mL) was added, followed by n-butyl lithium (102 mL) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was
30 repeated once. (2) Additional bromochloromethane (7 mL, 0.11 mol) was added, followed by n-butyl lithium (51 mL, 0.082 mol) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was repeated 5 times. (3) Additional bromochloromethane (7
35 mL, 0.11 mol) was added, followed by n-butyl lithium (51 mL, 0.082 mol) at < -25°C. After addition the mixture was stirred at -30 to -35°C for 10 minutes. This was

repeated once. The external cooling was stopped and the mixture warmed to ambient temp. over 4 to 16 hours when TLC (silica gel, 20% ethyl acetate/hexane) indicated that the reaction was completed. The reaction mixture was cooled to 10°C and quenched with 1452 g of 16% ammonium chloride solution (prepared by dissolving 232 g of ammonium chloride in 1220 mL of water), keeping the temperature below 23°C. The mixture was stirred for 10 minutes and the organic and aqueous layers were separated. The aqueous phase was extracted with ethyl acetate (2x 500 mL). The ethyl acetate layer was combined with the tetrahydrofuran layer. The combined solution was dried over magnesium sulfate (220 g), filtered and concentrated on a rotary evaporator at 65°C. The brown oil residue was dried at 70°C in vacuo (0.8 bar) for 1 h to give 222.8 g of crude material.

METHOD 4:

Following the same procedures as described in Method 3 of this Example except the reaction temperatures were at -20°C. The resulting N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was a diastereomeric mixture of lesser purity than that of Method 3.

METHOD 5:

Following the same procedures as described in Method 3 of this Example except the reaction temperatures were at -70--78°C. The resulting N,N,αS-tris(phenylmethyl)-2S-oxiranemethanamine was a diastereomeric mixture, which was used directly in the subsequent steps without purification.

METHOD 6:

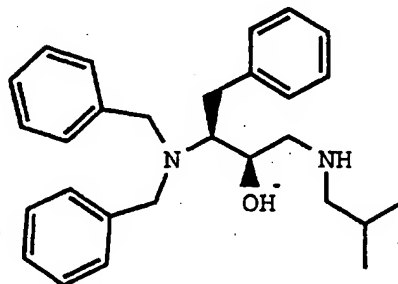
Following the same procedures as described in Method 3 of this Example except a continuous addition of bromochloromethane and n-butyl lithium was used at -30 to -35°C. After the reaction and work up procedures as

described in Method 3 of this Example, the desired N,N, α S-tris(phenylmethyl)-2S-oxiranemethanamine was isolated in comparable yields and purities.

5 METHOD 7:

Following the same procedures as described in Method 2 of this Example except dibromomethane was used instead of chloriodomethane. After the reaction and work up procedures as described in Method 2 of this Example, the
10 desired N,N, α S-tris(phenylmethyl)-2S-oxirane-methanamine was isolated.

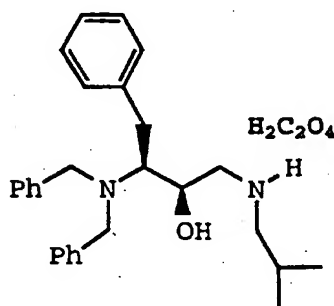
EXAMPLE 4



15 Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine

20 To a solution of crude N,N-dibenzyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane (388.5 g, 1.13 mol) in isopropanol (2.7 L) (or ethyl acetate) was added isobutylamine (1.7 kgm, 23.1 mol) over 2 min. The temperature increased from 25°C and to 30°C. The
25 solution was heated to 82°C and stirred at this temperature for 1.5 hours. The warm solution was concentrated under reduced pressure at 65°C. The brown oil residue was transferred to a 3-L flask and dried in vacuo (0.8 mm Hg) for 16 h to give 450 g of 3S-(N,N-bis(phenylmethyl)amino-4-phenylbutan-2R-ol as a crude
30 oil.

An analytical sample of the desired major diastereomeric product was obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane). Tlc analysis: silica gel, 40% ethyl acetate/hexane; $R_f = 0.28$; HPLC analysis: ultrasphere ODS column, 25% triethylamino-/phosphate buffer pH 3-acetonitrile, flow rate 1 mL/min, UV detector; retention time 7.49 min.; HRMS Calcd for $C_{28}H_{27}N_2O$ ($M + 1$) 417.616, found 417.2887. An analytical sample of the minor diastereomeric product, 3S-[N,N-bis(phenylmethyl)amino]1-(2-methylpropyl)amino-4-phenylbutan-2S-ol was also obtained by purifying a small sample of crude product by silica gel chromatography (40% ethyl acetate/hexane).

EXAMPLE 5

20

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine·oxalic acid salt

To a solution of oxalic acid (8.08g, 89.72 mmol) in methanol (76 mL) was added a solution of crude 3(S)-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (39.68g, which contains about 25.44g (61.06 mmol) of 3(S),2(R) isomer and about 4.49g (10.78 mmol) of 3(S),2(S) isomer) in ethyl acetate (90 mL) over 15 minutes. The mixture was stirred at room temperature for about 2 hours. Solid was isolated by filtration, washed

with ethyl acetate (2 x 20 mL) and dried in vacuo for about 1 hour to yield 21.86g (70.7% isomer recovery) of 97% diastereomerically pure salt (based on HPLC peak areas). HPLC analysis: Vydec-peptide/protein C18 column, UV detector 254 nm, flow rate 2 mL/min., gradient (A = 0.05% trifluoroacetic acid in water, B = 0.05% trifluoroacetic acid in acetonitrile, 0 min. 75% A/25% B, 30 min. 10% A/90% B, 35 min. 10% A/90% B, 37 min. 75% A/25% B); Retention time 10.68 min. (3(S),2(R) isomer) and 9.73 min. (3(S),2(S) isomer). Mp = 174.99°C; Microanalysis: Calc.: C 71.05%, H 7.50%, N 5.53%; Found: C 71.71%, H 7.75%, N 5.39%.

Alternatively, oxalic acid dihydrate (119g, 0.94 mole) was added to a 5000 mL round bottom flask fitted with a mechanical stirrer and a dropping funnel. Methanol (1000 ml) was added and the mixture stirred until dissolution was complete. A solution of crude 3(S)-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol in ethyl acetate (1800 ml, 0.212g amino alcohol isomers/mL, 0.9160 moles) was added over a twenty minute period. The mixture was stirred for 18 hours and the solid product was isolated by centrifugation in six portions at 400G. Each portion was washed with 125 mL of ethyl acetate. The salt was then collected and dried overnight at 1 torr to yield 336.3 g of product (71% based upon total amino alcohol). HPLC/MS (electrospray) was consistent with the desired product (m/z 417 [M+H]⁺).

Alternatively, crude 3(S)-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (5 g) was dissolved in methyl-tert-butylether (MTBE) (10 mL) and oxalic acid (1 g) in methanol (4 mL) was added. The mixture was stirred for about 2 hours. The resulting solid was filtered, washed with cold MTBE and dried to

yield 2.1 g of white solid of about 98.9%
diastereomerically pure (based on HPLC peak areas).

EXAMPLE 6

5

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)- hydroxy-4-phenylbutyl]-N-isobutylamine·acetic acid salt

To a solution of crude 3(S)-[N,N-bis(phenylmethyl)
10 amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol in
methyl-tert-butylether (MTBE) (45 mL, 1.1g amino alcohol
isomers/mL) was added acetic acid (6.9 mL) dropwise. The
mixture was stirred for about 1 hour at room temperature.
The solvent was removed in vacuo to yield a brown oil
15 about 85% diastereomerically pure product (based on HPLC
peak areas). The brown oil was crystallized as follows:
0.2 g of the oil was dissolved in the first solvent with
heat to obtain a clear solution, the second solvent was
added until the solution became cloudy, the mixture was
20 heated again to clarity, seeded with about 99%
diastereomerically pure product, cooled to room
temperature and then stored in a refrigerator overnight.
The crystals were filtered, washed with the second
solvent and dried. The diastereomeric purity of the
25 crystals was calculated from the HPLC peak areas. The
results are shown in Table 1.

TABLE 1

| First Solvent | Second Solvent | Solvent Ratio | Recovery Weight (g) | Diastereomeric Purity (%) |
|---------------|----------------|---------------|---------------------|---------------------------|
| MTBE | Heptane | 1:10 | 0.13 | 98.3 |
| MTBE | Hexane | 1:10 | 0.03 | 99.6 |
| Methanol | Water | 1:1.5 | 0.05 | 99.5 |
| Toluene | Heptane | 1:10 | 0.14 | 98.7 |
| Toluene | Hexane | 1:10 | 0.10 | 99.7 |

30

Alternatively, crude 3(S)-[N,N-bis(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (50.0g, which contains about 30.06g (76.95 mmol) of 3(S),2(R) isomer and about 5.66g (13.58 mmol) of 3(S),2(S) isomer) was dissolved in methyl-tert-butylether (45.0 mL). To this solution was added acetic acid (6.90 mL, 120.6 mmol) over a period of about 10 min. The mixture was stirred at room temperature for about 1 hour and concentrated under reduced pressure. The oily residue was purified by recrystallization from methyl-tert-butylether (32 mL) and heptane (320 mL). Solid was isolated by filtration, washed with cold heptane and dried in vacuo for about 1 hour to afford 21.34g (58.2% isomer recovery) of 96% diastereomerically pure monoacetic acid salt (based on HPLC peak areas). Mp = 105-106°C; Microanalysis: Calc.: C 75.53%, H 8.39%, N 5.87%; Found: C 75.05%, H 8.75%, N 5.71%.

EXAMPLE 7

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine·L-tartaric acid salt

Crude 3(S)-[N,N-bis(phenylmethyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (10.48g, which contains about 6.72g (16.13 mmol) of 3(S),2(R) isomer and about 1.19g (2.85 mmol) of 3(S),2(S) isomer) was dissolved in tetrahydrofuran (10.0 mL). To this solution was added a solution of L-tartaric acid (2.85g, 19 mmol) in methanol (5.0 mL) over a period of about 5 min. The mixture was stirred at room temperature for about 10 min. and concentrated under reduced pressure. Methyl-tert-butylether (20.0 mL) was added to the oily residue and the mixture was stirred at room temperature for about 1 hour. Solid was isolated by filtration to afford 7.50g of crude salt. The crude salt was purified by recrystallization from ethyl acetate and heptane at room

temperature to yield 4.13g (45.2% isomer recovery) of 95% diastereomerically pure L-tartaric acid salt (based on HPLC peak areas). Microanalysis: Calc.: C 67.76%, H 7.41%, N 4.94%; Found: C 70.06%, H 7.47%, N 5.07%.

5

EXAMPLE 8

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine·dihydrochloric acid salt

Crude 3(S)-[N,N-bis(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (10.0g, which contains about 6.41g (15.39 mmol) of 3(S),2(R) isomer and about 1.13g (2.72 mmol) of 3(S),2(S) isomer) was dissolved in tetrahydrofuran (20.0 mL). To this solution was added hydrochloric acid (20 mL, 6.0 N) over a period of about 5 min. The mixture was stirred at room temperature for about 1 hour and concentrated under reduced pressure. The residue was recrystallized from ethanol at 0°C to yield 3.20g (42.7% isomer recovery) of 98% diastereomerically pure dihydrochloric acid salt (based on HPLC peak areas). Microanalysis: Calc.: C 68.64%, H 7.76%, N 5.72%; Found: C 68.79%, H 8.07%, N 5.55%.

25

EXAMPLE 9

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine·toluenesulfonic acid salt

Crude 3(S)-[N,N-bis(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (5.0g, which contains about 3.18g (7.63 mmol) of 3(S),2(R) isomer and about 0.56g (1.35 mmol) of 3(S),2(S) isomer) was dissolved in methyl-tert-butylether (10.0 mL). To this solution was added a solution of toluenesulfonic acid

35

(2.28g, 12 mmol) in methyl-tert-butylether (2.0 mL) and methanol (2.0 mL) over a period of about 5 min. The mixture was stirred at room temperature for about 2 hours and concentrated under reduced pressure. The residue was recrystallized from methyl-tert-butylether and heptane at 0°C, filtered, washed with cold heptane and dried in vacuo to yield 1.85g (40.0% isomer recovery) of 97% diastereomerically pure monotoluenesulfonic acid salt (based on HPLC peak areas).

10

EXAMPLE 10

Preparation of N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine-methanesulfonic acid salt

15

Crude 3(S)-[N,N-bis(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2(R)-ol (10.68g, which contains about 6.85g (16.44 mmol) of 3(S),2(R) isomer and about 1.21g (2.90 mmol) of 3(S),2(S) isomer) was dissolved in tetrahydrofuran (10.0 mL). To this solution was added methanesulfonic acid (1.25 mL, 19.26 mmol). The mixture was stirred at room temperature for about 2 hours and concentrated under reduced pressure. The oily residue was recrystallized from methanol and water at 0°C, filtered, washed with cold methanol/water (1:4) and dried in vacuo to yield 2.40g (28.5% isomer recovery) of 98% diastereomerically pure monomethanesulfonic acid salt (based on HPLC peak areas).

25
30

EXAMPLE 11

Preparation of N-benzyl-L-phenylalaninol

35 METHOD 1:

L-Phenylalaninol (89.51 g, 0.592 moles) was dissolved in 375 mL of methanol under inert atmosphere,

35.52 g (0.592 moles) of glacial acetic acid and 50 mL of methanol was added followed by a solution of 62.83 g (0.592 moles) of benzaldehyde in 100 mL of methanol. The mixture was cooled to approximately 15°C and a solution of 134.6 g (2.14 moles) of sodium cyanoborohydride in 700 mL of methanol was added in approximately 40 minutes, keeping the temperature between 15°C and 25°C. The mixture was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and partitioned between 1 L of 2M ammonium hydroxide solution and 2 L of ether. The ether layer was washed with 1 L of 1M ammonium hydroxide solution, twice with 500 mL water, 500 mL of brine and dried over magnesium sulfate for 1 hour. The ether layer was filtered, concentrated under reduced pressure and the crude solid product was recrystallized from 110 mL of ethyl acetate and 1.3 L of hexane to give 115 g (81% yield) of N-benzyl-L-phenylalaninol as a white solid.

METHOD 2:

L-Phenylalaninol (5 g, 33 mmol) and 3.59 g (33.83 mmol) of benzaldehyde were dissolved in 55 mL of 3A ethanol under inert atmosphere in a Parr shaker and the mixture was warmed to 60°C for 2.7 hours. The mixture was cooled to approximately 25°C and 0.99 g of 5% platinum on carbon was added and the mixture was hydrogenated at 60 psi of hydrogen and 40°C for 10 hours. The catalyst was filtered off, the product was concentrated under reduced pressure and the crude solid product was recrystallized from 150 mL of heptane to give 3.83 g (48 % yield) of N-benzyl-L-phenylalaninol as a white solid.

EXAMPLE 12

35

Preparation of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninol

N-benzyl-L-phenylalaninol (2.9 g, 12 mmoles) was dissolved in 3 mL of triethylamine and 27 mL of methanol and 5.25 g (24.1 mmoles) of di-tert-butyl dicarbonate was added. The mixture was warmed to 60°C for 35 minutes and concentrated under reduced pressure. The residue was dissolved in 150 mL of ethyl acetate and washed twice with 10 mL of cold (0-5°C), dilute hydrochloric acid (pH 2.5 to 3), 15 mL of water, 10 mL of brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product oil was purified by silica gel chromatography (ethyl acetate: hexane, 12:3 as eluting solvent) to give 3.98 g (97% yield) of colorless oil.

15

EXAMPLE 13Preparation of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninal

20 METHOD 1:

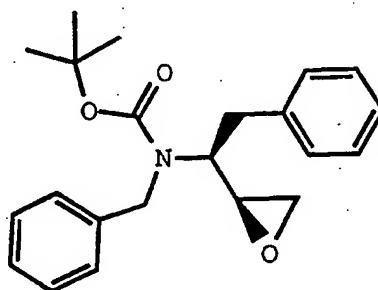
To a solution of 0.32 g (0.94 mmoles) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninol in 2.8 mL of toluene was added 2.4 mg (0.015 mmoles) of 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO), 0.1g (0.97 mmoles) of sodium bromide, 2.8 mL of ethyl acetate and 0.34 mL of water. The mixture was cooled to 0°C and an aqueous solution of 4.2 mL of 5% household bleach containing 0.23 g (3.0 mL, 2.738 mmoles) of sodium bicarbonate was added slowly over 30 minutes. The mixture was stirred at 0°C for 10 minutes. Three more additions (0.4 mL each) of bleach was added followed by stirring for 10 minutes after each addition to consume all the starting material. The two phase mixture was allowed to separate. The aqueous layer was extracted twice with 8 mL of toluene. The combined organic layer was washed with 1.25 mL of a solution containing 0.075 g of potassium iodide, sodium bisulfate (0.125 g) and

water (1.1 mL), 1.25 mL of 10% aqueous sodium thiosulfate solution, 1.25 mL of pH 7 phosphate buffer and 1.5 mL of brine solution. The organic solution was dried over magnesium sulfate, filtered and concentrated under reduced pressure to give 0.32 g (100% yield) of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninal.

METHOD 2:

To a solution of 2.38 g (6.98 mmol) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninol in 3.8 mL (27.2 mmol) of triethylamine at 10 °C was added a solution of 4.33 g (27.2 mmol) of sulfur trioxide pyridine complex in 17 mL of dimethyl sulfoxide. The mixture was warmed to room temperature and stirred for one hour. Water (16 mL) was added and the mixture was extracted with 20 mL of ethyl acetate. The organic layer was washed with 20 mL of 5% citric acid, 20 mL of water, 20 mL of brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give 2.37 g (100% yield) of N-(t-Butoxycarbonyl)-N-benzyl-L-phenylalaninal.

EXAMPLE 14



25

Preparation of 3(S)-[N-(t-butoxycarbonyl)-N-benzylaminol]-1,2-(S)-epoxy-4-phenylbutane

METHOD 1:

A solution of 2.5 g (7.37 mmol) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal and 0.72 mL of

chloriodomethane in 35 mL of THF was cooled to -78°C. A 4.64 mL of a solution of n-butyllithium (1.6 M in hexane, 7.42 mmoles) was added slowly, keeping the temperature below -70°C. The mixture was stirred for 10 minutes
5 between -70 to -75°C. Two additional portions of 0.22 mL of chloriodomethane and 1.4 mL of n-butyllithium was added sequentially and the mixture was stirred for 10 minutes between -70 to -75°C after each addition. Four
10 additional portions of 0.11 mL of chloriodomethane and 0.7 mL of n-butyllithium was added sequentially and the mixture was stirred for 10 minutes between -70 to -75°C after each addition. The mixture was warmed to room temperature for 3.5 hours. The product was quenched at below 5°C with 24 mL of ice-cold water. The biphasic
15 layers were separated and the aqueous layer was extracted twice with 30 mL of ethyl acetate. The combined organic layers was washed three times with 10 mL water, then with 10 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2.8 g of a
20 yellow crude oil. This crude oil (>100% yield) is a mixture of the diastereomeric epoxides N,αS-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N,αS-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine. The crude mixture
25 is used directly in the next step without purification.

METHOD 2:

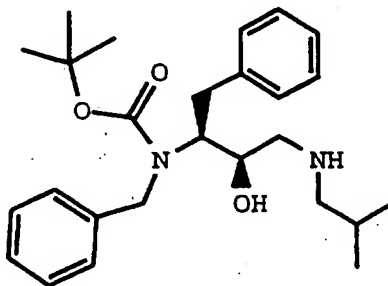
To a suspension of 2.92 g (13.28 mmoles) of trimethylsulfoxonium iodide in 45 mL of acetonitrile was
30 added 1.49 g (13.28 mmoles) of potassium t-butoxide. A solution of 3.0 g (8.85 mmoles) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal in 18 mL of acetonitrile was added and the mixture was stirred at room temperature for one hour. The mixture was diluted with 150 mL of water
35 and extracted twice with 200 mL of ethyl acetate. The organic layers were combined and washed with 100 mL water, 50 mL brine, dried over sodium sulfate, filtered

and concentrated under reduced pressure to give 3.0 g of a yellow crude oil. The crude product was purified by silica gel chromatography (ethyl acetate/hexane: 1: 8 as eluting solvent) to give 1.02 g (32.7% yield) of a mixture of the two diastereomers N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine.

10 METHOD 3:

To a suspension of 0.90 g (4.42 mmol) of trimethylsulfonium iodide in 18 mL of acetonitrile was added 0.495 g (4.42 mmol) of potassium t-butoxide. A solution of 1.0 g (2.95 mmol) of N-(t-butoxycarbonyl)-N-benzyl-L-phenylalaninal in 7 mL of acetonitrile was added and the mixture was stirred at room temperature for one hour. The mixture was diluted with 80 mL of water and extracted twice with 80 mL of ethyl acetate. The organic layers were combined and washed with 100 mL water, 30 mL brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1.04 g of a yellow crude oil. The crude product was a mixture of the two diastereomers N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine.

EXAMPLE 15

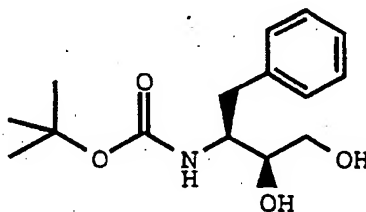


Preparation of 3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

To a solution of 500 mg (1.42 mmoles) of the crude epoxide (a mixture of the two diastereomers N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxiranemethanamine and N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2R-oxiranemethanamine in 0.98 mL of isopropanol was added 0.71 mL (7.14 mmoles) of isobutylamine. The mixture was warmed to reflux at 85°C to 90°C for 1.5 hours. The mixture was concentrated under reduced pressure and the product oil was purified by silica gel chromatography (chloroform:methanol, 100:6 as eluting solvents) to give 330 mg of 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a colorless oil (54.5% yield). 3S-[N-(t-Butoxycarbonyl)-N-(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2S-ol was also isolated. When purified N, α S-bis(phenylmethyl)-N-(t-butoxycarbonyl)-2S-oxirane methanamine was used as starting material, 3S-[N-(t-butoxycarbonyl)-N-(phenylmethyl) amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol was isolated after purification by chromatography in an 86% yield.

25

EXAMPLE 16



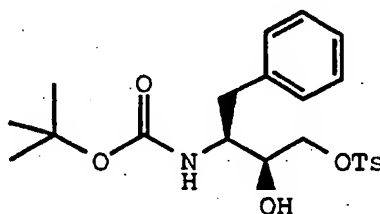
Preparation of 3S-(N-t-Butoxycarbonyl)amino-4-phenylbutan-1,2R-diol

30

To a solution of 1 g (3.39 mmoles) of 2S-(N-t-butoxycarbonyl)amino-1S-hydroxy-3-phenylbutanoic acid

(commercially available from Nippon Kayaku, Japan) in 50 mL of THF at 0 °C was added 50 mL of borane-THF complex (liquid, 1.0 M in THF), keeping the temperatures below 5°C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The mixture was cooled to 0 °C and 20 mL of water was added slowly to destroy the excess BH₃ and to quench the product mixture, keeping the temperature below 12°C. The quenched mixture was stirred for 20 minutes and concentrated under reduced pressure. The product mixture was extracted three times with 60 mL of ethyl acetate. The organic layers were combined and washed with 20 mL of water, 25 mL of saturated sodium chloride solution and concentrated under reduced pressure to give 1.1 g of crude oil. The crude product was purified by silica gel chromatography (chloroform/methanol, 10:6 as eluting solvents) to give 900 mg (94.4% yield) of 3S-(N-t-butoxycarbonyl)amino-4-phenylbutan-1,2R-diol as a white solid.

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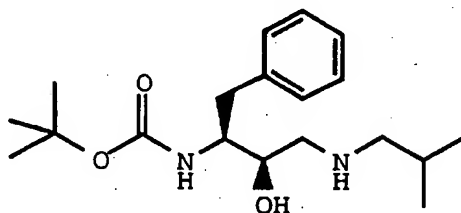
EXAMPLE 17

25 Preparation of 3S-(N-t-Butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl Toluenesulfonate

To a solution of 744.8 mg (2.65 mmoles) of 3S-(N-t-butoxycarbonyl)amino-4-phenylbutan-1,2R-diol in 13 mL of pyridine at 0 °C was added 914 mg of toluenesulfonyl chloride in one portion. The mixture was stirred at 0 °C to 5°C for 5 hours. A mixture of 6.5 mL of ethyl acetate and 15 mL of 5% aqueous sodium bicarbonate solution was added to the reaction mixture and stirred for 5 minutes.

The product mixture was extracted three times with 50 mL of ethyl acetate. The organic layers were combined and washed with 15 mL of water, 10 mL of saturated sodium chloride solution and concentrated under reduced pressure to give about 1.1 g of a yellow chunky solid. The crude product was purified by silica gel chromatography (ethyl acetate/hexane 1:3 as eluting solvents) to give 850 mg (74% yield) of 3S-(N-t-butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl toluenesulfonate as a white solid.

EXAMPLE 18

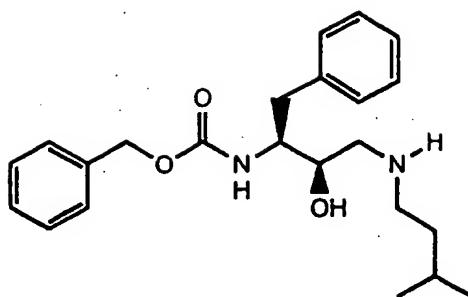


15 Preparation of 3S-[N-(t-Butoxycarbonyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol

To a solution of 90 mg (0.207 mmoles) of 3S-(N-t-butoxycarbonyl)amino-2R-hydroxy-4-phenylbut-1-yl toluenesulfonate in 0.143 mL of isopropanol and 0.5 mL of toluene was added 0.103 mL (1.034 mmoles) of isobutylamine. The mixture was warmed to 80 to 85 °C and stirred for 1.5 hours. The product mixture was concentrated under reduced pressure at 40 to 50 °C and purified by silica gel chromatography (chloroform/methanol, 10:1 as eluting solvents) to give 54.9 mg (76.8% yield) of 3S-[N-(t-butoxycarbonyl)amino]-1-(2-methylpropyl)amino-4-phenylbutan-2R-ol as a white solid.

EXAMPLE 19

Preparation of N-[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine



Part A:

- 5 To a solution of 75.0g (0.226 mol) of N-benzyloxy carbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The
- 10 solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over
- 15 anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane.
- 20 The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+ = 340$.

25 Part B:

- To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for
- 30 fifteen minutes, the solvent was removed in vacuo. The residue was dissolved in methylene chloride, washed with water, dried (magnesium sulfate), filtered and stripped

to yield 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH⁺ 298.

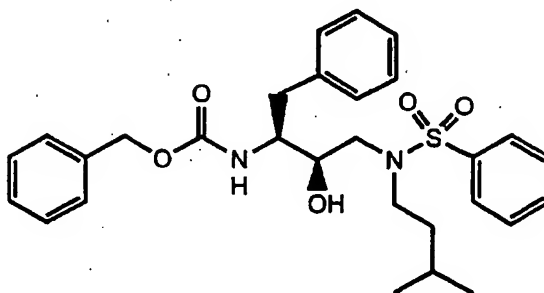
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Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 1.18g, 95% of N=[3(S)-phenylmethylcarbamoyl]amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine mp 108.0-109.5°C, MH⁺ m/z = 371.

20

EXAMPLE 20



25

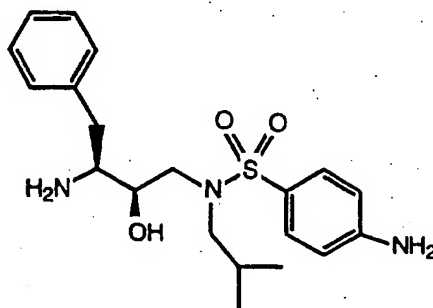
Preparation of phenylmethyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

From the reaction of N-[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]isoamylamine (1.47 gm, 3.8 mmol), triethylamine (528 uL, 3.8 mmol) and benzene sulfonyl chloride (483 uL, 3.8 mmol) one obtains benzyl [2R-hydroxy-3-[(3-methylbutyl) (phenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate. Column chromatography on

30

silica gel eluting with chloroform containing 1% ethanol afforded the pure product. Anal. Calcd for $C_{29}H_{36}N_2O_5S$: C, 66.39; H, 6.92; N, 5.34. Found: C, 66.37; H, 6.93; N, 5.26.

5

EXAMPLE 21

10 Preparation of 2R-hydroxy-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

Part A: Preparation of Carbamic acid, 2R-hydroxy-3-[[[4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-

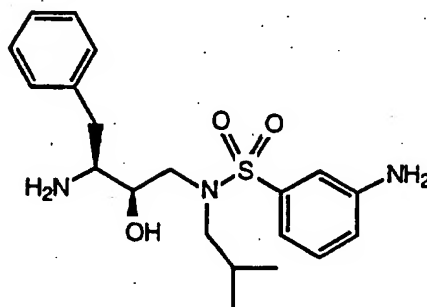
15 (phenylmethyl)propyl-, phenylmethyl ester

To a solution of 4.0 g (10.8 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 50mL of anhydrous methylene chloride, was added 4.5mL
 20 (3.27g, 32.4 mmol) of triethylamine. The solution was cooled to 0°C and 2.63g (11.9 mmol) of 4-nitrobenzene sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium
 25 bicarbonate, brine, dried and concentrated to yield 5.9 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 4.7 g of pure carbamic acid, [2R-hydroxy-3-[[[4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester,
 30 m/e=556(M+H).

Part B: Preparation of 2R-hydroxy-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

- 5 A solution of 3.0g (5.4 mmol) of carbamic acid, 2R-hydroxy-3-[[[(4-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 20 mL of ethyl acetate was hydrogenated over 1.5 g of 10% palladium-on-carbon catalyst under 35 psig of hydrogen
10 for 3.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 2.05 g of the desired 2R-hydroxy-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine, m/e=392 (M+H).

15

EXAMPLE 22

- 20 Preparation of 2R-hydroxy-3-[[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

Part A: Preparation of Carbamic acid, [2R-hydroxy-3-[[[(3-nitrophenyl)sulfonyl](2-methylpropyl)amino]-1S-

- 25 (phenylmethyl)propyl-, phenylmethyl ester

To a solution of 1.1 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 15mL of anhydrous methylene chloride, was added 1.3mL
30 (0.94g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.67 g (3.0 mmol) of 3-nitrobenzene

sulfonyl chloride was added, stirred for 30 minutes at 0°C, then for 1 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.74 g of crude material. This was recrystallized from ethyl acetate/hexane to afford 1.40 g of pure carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester, m/e=562 (M+Li).

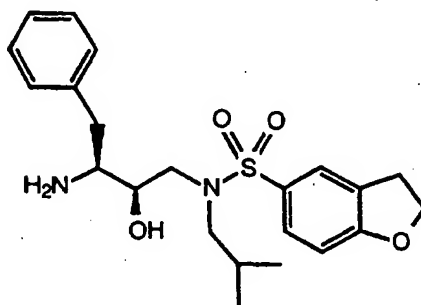
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Part B: Preparation of [2R-hydroxy-3-[[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

15 A solution of 1.33g (2.5 mmol) of carbamic acid, [2R-hydroxy-3-[(3-nitrophenylsulfonyl)(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 40 mL of 1:1 methanol/tetrahydrofuran was hydrogenated over 0.70 g of 10% palladium-on-carbon catalyst under 40 psig of
20 hydrogen for 1.5 hours. The catalyst was removed by filtration and the solution concentrated to afford 0.87 g of the desired [2R-hydroxy-3-[[[(3-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

25

EXAMPLE 23



30 Preparation of 2R-hydroxy-3-[[[(2,3-dihydrobenzofuran-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

Part A: Preparation of 5-(2,3-dihydrobenzofuranyl)
sulfonyl chloride

- 5 To a solution of 3.35g of anhydrous N,N-dimethylformamide at 0°C under nitrogen was added 6.18 g of sulfonyl chloride, whereupon a solid formed. After stirring for 15 minutes, 4.69 g of 2,3-dihydrobenzofuran was added, and the mixture heated at 100°C for 2 hours. The
10 reaction was cooled, poured into ice water, extracted with methylene chloride, dried over magnesium sulfate, filtered and concentrated the crude material. This was recrystallized from ethyl acetate to afford 2.45 g of 5-(2,3-dihydrobenzofuranyl)sulfonyl chloride.

15

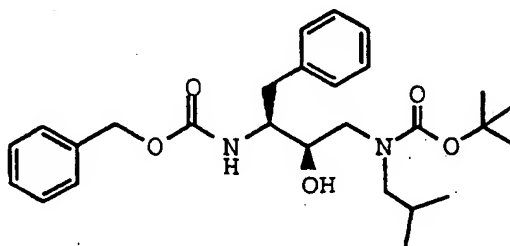
Part B: Preparation of Carbamic acid, 2R-hydroxy-3-
[[(2,3-dihydrobenzofuran-5-yl)sulfonyl] (2-methylpropyl)
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

- 20 To a solution of 1.11 g (3.0 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 20mL of anhydrous methylene chloride, was added 1.3mL (0.94 g, 9.3 mmol) of triethylamine. The solution was cooled to 0°C and 0.66 g of 5-(2,3-dihydrobenzofuranyl)
25 sulfonyl chloride was added, stirred for 15 minutes at 0°C, then for 2 hour at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield 1.62 g of crude material. This was recrystallized from
30 diethyl ether to afford 1.17 g of pure carbamic acid, [2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl] (2-methylpropyl) amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester.

- 35 Part C: Preparation of [2R-hydroxy-3-[[(2,3-dihydro benzofuran-5-yl)sulfonyl] (2-methylpropyl) amino]-1S-(phenylmethyl)propylamine

A solution of 2.86 g of carbamic acid, [2R-hydroxy-3-
[[(2,3-dihydrobenzofuran-5-yl)sulfonyl] (2-methylpropyl)
amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 30
5 mL of tetrahydrofuran was hydrogenated 0.99g of 10%
palladium-on-carbon under 50 psig of hydrogen for 16
hours. The catalyst was removed by filtration and the
filtrate concentrated to afford 1.99 g of the desired
[2R-hydroxy-3-[[(2,3-dihydrobenzofuran-5-yl)sulfonyl] (2-
10 methylpropyl) amino]-1S-(phenylmethyl)propylamine.

EXAMPLE 24



15

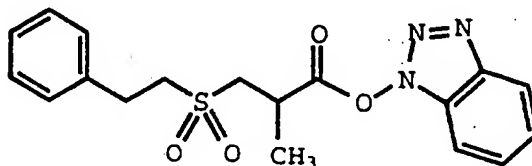
Preparation of N-[(1,1-dimethylethoxycarbonyl)amino]-N-[2-
methylpropyl]-3S-[N1-(phenylmethoxycarbonyl)amino]-2R-
hydroxy-4-phenylbutylamine

20 To a solution of 7.51g (20.3 mmol) of N-[3S-
[(phenylmethoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-
2-methylpropylamine in 67 mL of anhydrous tetrahydrofuran
was added 2.25g (22.3 mmol) of triethylamine. After
cooling to 0°C, 4.4g (20.3 mmol) of di-tert-butyl
25 dicarbonate was added and stirring continued at room
temperature for 21 hours. The volatiles were removed in
vacuo, ethyl acetate added, then washed with 5% citric
acid, saturated sodium bicarbonate, brine, dried over
magnesium sulfate, filtered and concentrated to afford
30 9.6g of crude product. Chromatography on silica gel
using 30% ethyl acetate/hexane afforded 8.2g of pure N-
[[3S-(phenylmethylcarbamoyl)amino]-2R-hydroxy-4-phenyl]-

1-[(2-methylpropyl)amino-2-(1,1-dimethylethoxyl)carbonyl]butane, mass spectrum $m/e = 477$ ($M+Li$).

EXAMPLE 25

5



Preparation of 2-methyl-3-[(2-phenylethyl)sulfonyl]propionic acid N-hydroxybenzotriazole ester

10

Part A: A solution of methyl methacrylate (7.25 g, 72.5 mmol) and phenethyl mercaptan (10.0 g, 72.5 mmol) in 100 mL of methanol was cooled in an ice bath and treated with sodium methoxide (100 mg, 1.85 mmol). The solution was stirred under nitrogen for 3 h and then concentrated in vacuo to give an oil that was taken up in ether and washed with 1 N aqueous potassium hydrogen sulfate, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated to give 16.83 g, 97.5% of methyl 2-(R,S)-methyl-4-thia-6-phenyl hexanoate as an oil. TLC on SiO₂ eluting with 20:1 hexane:ethyl acetate (v:v) $R_f=0.41$. Alternatively, one can use methyl 3-bromo-2-methyl propionate in place of methyl methacrylate.

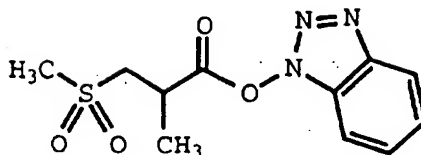
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Part B: A solution of methyl 2-(R,S)-methyl-4-thia-6-phenyl hexanoate (4.00 g, 16.8 mmol) in 100 mL of dichloromethane was stirred at room temperature and treated portion wise with meta-chloroperoxybenzoic acid (7.38 g, 39.2 mmol) over approximately 40 m. The solution was stirred at room temperature for 16 h and then filtered and the filtrate washed with saturated aqueous sodium bicarbonate, 1N sodium hydroxide, saturated aqueous sodium chloride, dried over anhydrous

30

magnesium sulfate, filtered, and concentrated to give 4.50 g, 99% of desired sulfone. The unpurified sulfone was dissolved in 100 mL of tetrahydrofuran and treated with a solution of lithium hydroxide (1.04 g, 24.5 mmol) in 40 mL of water. The solution was stirred at room temperature for 2 m and then concentrated in vacuo. The residue was then acidified with 1N aqueous potassium hydrogen sulfate to pH=1 and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated to give a white solid. The solid was taken up in boiling ethyl acetate/hexane and allowed to stand undisturbed whereupon white needles formed that were isolated by filtration and air dried to give 3.38 g, 79% of 2-(R,S)-methyl-3(β -phenethylsulfonyl)-propionic acid, mp 91-93°C.

Part C: A solution of 2-(R,S)-methyl-3(β -phenethylsulfonyl)-propionic acid (166.1 mg, 0.65 mmol), N-hydroxybenzotriazole (HOBT) (146.9 mg, 0.97 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (145.8 mg, 0.75 mmol) in 4 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution is then treated with a desired protected amino or sulfonamide isostere intermediate and stirred at room temperature for 16 h. The solution is poured into 30 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution is then decanted from the organic residue. The organic residue is taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography of the mixture on silica gel eluting with 1:1 hexane:ethyl acetate can be utilized and will afford the separated diastereomers.

EXAMPLE 26

5 Preparation of 2-methyl-3-(methanesulfonyl)propionic acid
10 N-hydroxybenzotriazole ester

Part A: A solution of methyl 2-(bromomethyl)-acrylate (26.4 g, 0.148 mol) in 100 mL of methanol was treated
10 with sodium methanesulfinate (15.1 g, 0.148 mol) portion
wise over 10 m at room temperature. The solution was
then stirred at room temperature for a period of 1.25 h
and the solution concentrated in vacuo. The residue was
15 then taken up in water and extracted four times with
ethyl acetate. The combined ethyl acetate solution was
washed with saturated sodium chloride, dried over
anhydrous magnesium sulfate, filtered and concentrated to
give a white solid, 20.7 g which was taken up in boiling
acetone/methyl tert-butyl ether and allowed to stand
20 whereupon crystals of pure methyl
2-(methanesulfonylmethyl) acrylate 18.0 g, 68% formed, mp
65-68 °C.

Part B: A solution of methyl 2-(methanesulfonylmethyl)
25 acrylate (970 mg, 5.44 mmol) in 15 mL of tetrahydrofuran
was treated with a solution of lithium hydroxide (270 mg,
6.4 mmol) in 7 mL of water. The solution was stirred at
room temperature for 5 m and then acidified to pH=1 with
1 N aqueous potassium hydrogen sulfate and the solution
30 extracted three times with ethyl acetate. The combined
ethyl acetate solution was dried over anhydrous magnesium
sulfate, filtered, and concentrated to give 793 mg, 89%
of 2-(methanesulfonylmethyl)acrylic acid, mp 147-149 °C.

Part C: A solution of 2-(methylsulfonylmethyl) acrylic acid (700 mg, 4.26 mmol) in 20 mL of methanol was charged into a Fisher-Porter bottle along with 10% palladium on carbon catalyst under a nitrogen atmosphere. The
5 reaction vessel was sealed and flushed five times with nitrogen and then five times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtered through a pad of celite to remove the catalyst and the
10 filtrate concentrated in vacuo to give 682 mg 96% of 2-(R,S)-methyl-3-methylsulfonyl propionic acid.

Part D: A solution of 2-(R,S)-methyl-3(methylsulfonyl) propionic acid (263.5 mg, 1.585 mmol),
15 N-hydroxybenzotriazole (HOBT) (322.2 mg, 2.13 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (339.1 mg, 1.74 mmol) in 4 mL of anhydrous dimethylformamide (DMF) is cooled to 0°C and stirred under nitrogen for 0.5 h. This solution is then
20 treated with a desired protected amino or sulfonamide isostere intermediate and stirred at room temperature for 16h. The solution is poured into 60 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution is then decanted from the organic residue. The
25 organic residue is taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give the desired product.

30

EXAMPLE 27Preparation of Sulfone Inhibitors From L-(+)-S-acetyl-β-mercaptoisobutyric Acid

35 Part A: A round-bottomed flask is charged with the desired protected amino or sulfonamide isostere intermediate (2.575 mmol) and coupled to L-(+)-S-acetyl-

b-mercapto butyric acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (339.1 mg, 1.74 mmol), in 10 mL of CH₂Cl₂ and is allowed to stir at room temperature for 16 h. The solution is concentrated in vacuo and the residue taken up in ethyl acetate, washed with 1N KHSO₄ sat. aq. NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and concentrated to give an oil which can be purified by radial chromatography on SiO₂ eluting with ethyl acetate to give the pure product.

Part B: A solution of the product of Part A (0.85 mmol) in 10 mL of methanol is treated with anhydrous ammonia for ca. 1 m at 0°C. The solution is stirred at that temperature for 16 h and then concentrated in vacuo to give the desired product that can be used directly in the next step without further purification.

Part C: A solution of the product of Part B (0.841 mmol) in 10 mL of dry toluene under nitrogen is treated in rapid succession with 1,8-diazabicyclo[5.4.0]undec-7-ene, (DBU), (128.1 mg, 0.841 mmol) and iodomethane (119.0 mg, 0.841 mmol). After 0.5 h at room temperature the reaction is diluted with ethyl acetate washed with 1N KHSO₄, sat. aq. NaHCO₃, brine. After the solution is dried over anhydrous MgSO₄, filtered and concentrated in vacuo the desired product is obtained and can be used directly in the next step.

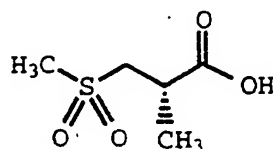
Part D: A solution of the product of Part C (0.73 mmol) and sodium perborate (500 mg, 3.25 mmol) in 30 mL of glacial acetic acid is warmed to 55°C for 16 h. The solution is concentrated in vacuo and then the residue is taken up in ethyl acetate, washed with water, sat. aq. NaHCO₃, brine, dried over anhydrous MgSO₄, filtered and concentrated to give the desired product.

General Procedure for Coupling Sulfonyl Compounds to
Sulfonamides

A mixture of the sulfonyl alkanoyl compound
5 (approximately 1 mmol), N-hydroxybenzotriazole (1.5
mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (EDC) (1.2 mmol) is dissolved in a suitable
solvent such as DMF and allowed to react for about 30
min. at 0°C. A desired protected amino or sulfonamide
10 isostere intermediate (1.05 mmol) is dissolved in DMF,
added to the above mixture and stirred at room
temperature for a period of time sufficient for the
reaction to take place. The solution is then poured into
saturated aqueous NaHCO₃ and extracted with, for example,
15 ethyl acetate. The extracts are washed, dried, filtered
and concentrated. The resulting material is then
crystallized from a suitable solvent or solvent mixture
such as hexanes and ethyl acetate to produce the product.

20

EXAMPLE 28



Preparation of 2(S)-methyl-3-(methylsulfonyl)propionic
25 Acid

Part A: To a solution of 10g of D-(-)-S-benzoyl-b-
mercaptioisobutyric acid t-butyl ester in 20 mL of
methanol was bubbled in gaseous ammonia at 0°C. The
30 reaction was allowed to then warm to room temperature,
stirred overnight and concentrated under reduced
pressure. The resulting mixture of a solid (benzamide)
and liquid was filtered to provide 5.21g of a pale oil
which then solidified. This was identified as 2(S)-
35 methyl-3-mercaptopropionic acid t-butyl ester.

Part B: To a solution of 5.21g of 2(S)-methyl-3-mercaptopropionic acid t-butyl ester in 75 mL of toluene at 0°C was added 4.50g of 1,8-diazabicyclo[5.4.0]undec-7-ene and 1.94 mL of methyl iodide. After stirring at room temperature for 2.5 hours, the volatiles were removed, ethyl acetate added, washed with dilute hydrochloric acid, water, brine, dried and concentrated to afford 2.82g of a pale oil, identified as 2(S)-methyl-3-(thiomethyl)propionic acid t-butyl ester.

Part C: To a solution of 2.82g of 2(S)-methyl-3-(thiomethyl)propionic acid t-butyl ester in 50 mL of acetic acid was added 5.58g of sodium perborate and the mixture heated to 55°C for 17 hours. The reaction was poured into water, extracted with methylene chloride, washed with aqueous sodium bicarbonate, dried and concentrated to afford 2.68g of 2(S)-methyl-3-(methylsulfonyl)propionic acid t-butyl ester as a white solid.

Part D: To 2.68g of 2(S)-methyl-3-(methylsulfonyl)propionic acid t-butyl ester was added 20 mL of 4N hydrochloric acid/dioxane and the mixture stirred at room temperature for 19 hours. The solvent was removed under reduced pressure to afford 2.18g of crude product, which was recrystallized from ethyl acetate/hexane to yield 1.44g of 2(S)-methyl-3-(methylsulfonyl)propionic acid as white crystals.

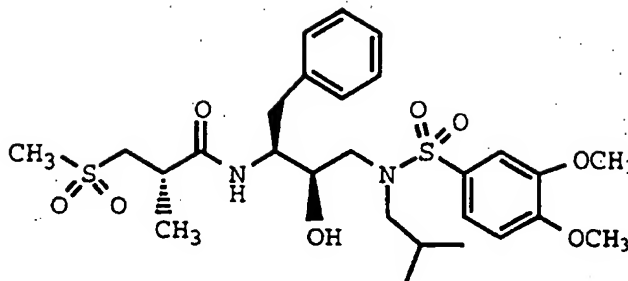
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EXAMPLE 29

Preparation of [1S-[1R*(R*),2S*]]-N-[2-hydroxy-3-[(2-methylpropyl)(3,4-dimethoxyphenylsulfonyl)amino]-1-(phenylmethyl)propyl]-2-methyl-3-(methylsulfonyl)propanamide

35

92



- Part A: A solution of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (50.0 g, 0.168 mol) and isobutylamine (246 g, 3.24 mol, 20 equivalents) in 650 mL of isopropyl alcohol was heated to reflux for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 57.56 g, 92% of N-[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine, mp 108.0-109.5 °C, MH+ m/z=371.
- Part B: A solution of N-[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine (1.5356 g, 4.14 mmol) and triethylamine (522 mg, 5.17 mmol) in 15 mL of dichloromethane was treated with 3,4-dimethoxybenzenesulfonyl chloride (1.0087 g, 4.26 mmol) at room temperature for 14h. The solvent was removed in vacuo and the residue taken up in ethyl acetate and then washed with 1N KHSO₄, saturated aqueous NaHCO₃, brine, dried over anhyd MgSO₄, filtered and concentrated to give 2.147 g, 90.5%, of a white solid, mp 124-127° C, HRFAB MS; M+Li; calc'd. for C₃₀H₃₈N₂O₇S+Li: 577.2560. Found: 577.2604.

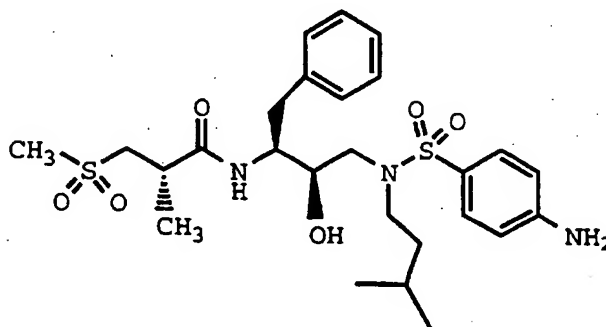
Part C: A solution of carbamic acid, product from Part B (513 mg, 0.90 mmol) in 30 mL of methanol was stirred with 20 mg of palladium black catalyst and 10 mL of formic acid for 15h at room temperature. The catalyst was

removed by filtration through diatomaceous earth and the filtrate concentrated in vacuo and the residue taken up in ethyl acetate. The ethyl acetate solution was washed with saturated aqueous NaHCO_3 , brine and dried over anhyd MgSO_4 , filtered and concentrated in vacuo to give a white solid, 386 mg, 98%, mp 123-130° C, FAB MS; $\text{M}+\text{Li}^+=443$, that was used directly in the next step without further purification.

- 10 Part D: A mixture of 2(S)-methyl-3-methylsulfonyl propionic acid (128 mg, 0.77 mmol), N-hydroxybenzotriazole (179.9 mg, 1.17 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (177.3 mg, 0.92 mmol) was dissolved in 1.5 mL of dimethylformamide (DMF) and allowed to react for 30 min at 0°C. The amine from Part C (359 mg, 0.82 mmol) dissolved in 1 mL of DMF was added to the above mixture and stirred at room temperature for 48h. The solution was then poured into 75 mL of saturated aqueous NaHCO_3 and extracted with ethyl acetate. The ethyl acetate extracts were washed with 5% aqueous citric acid, saturated aqueous NaHCO_3 , brine, dried over anhyd MgSO_4 , filtered and concentrated to give a clear oil, 220 mg. The material was crystallized from hexanes and ethyl acetate to give 178 mg, 40% of pure product with mp 130-133°C. HRFAB MS; $\text{M}+\text{Li}^+$; calc'd. for $\text{C}_{27}\text{H}_{40}\text{N}_2\text{O}_8\text{S}_2\text{Li}$: 591.2386. Found: 591.2396.

EXAMPLE 30

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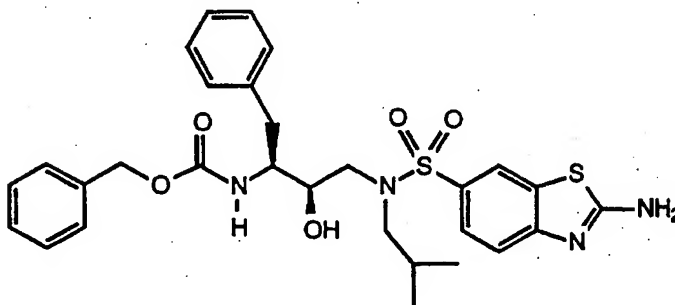
Preparation of [1S-[1R*(R*),2S*]]-N-[2-hydroxy-3-[(3-methylbutyl)(4-aminophenylsulfonyl)amino]-1-(phenylmethyl)propyl]-2-methyl-3-(methylsulfonyl)propanamide

- Part A: A solution of N-benzyloxycarbonyl-3(S)-amino-1,2(S)epoxy-4-phenylbutane (11.54 g, 38.81 mmol) and isoamylamine (66.90 g, 0.767 mol, 19.9 equivalents) in 90 mL of isopropyl alcohol was heated to reflux for 3.1h. The solution was cooled to room temperature and partially concentrated in vacuo and the remaining solution poured into 200 mL of stirring hexanes whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 11.76 g, 79% of N-[[3(S)-phenylmethoxy)carbonyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine, mp 118-122° C, FAB MS: MH+=385.
- Part B: A solution of N-[[3(S)-(phenylmethoxycarbonyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine (1.1812 g, 3.07 mmol) and triethylamine (325.7 mg, 3.22 mmol) in 20 mL of dichloromethane was treated with 4-nitrobenzensulfonyl chloride (767 mg, 90% purity 3.11 mmol) at room temperature for 10 min. The solvent was removed in vacuo and the residue taken up in ethyl acetate and then washed with 1N KHSO₄, saturated aqueous NaHCO₃, brine, dried over anhyd MgSO₄, filtered and concentrated to give 2.3230 g, of a tan solid, that was crystallized from ethyl acetate and petroleum ether to provide 870 mg, 50%, mp 130-132° C of pure product, HRFAB MS; M+Li, calc'd. for C₂₉H₃₅N₃O₇SLi: 576.2316. Found: 576.2350.
- Part C: A solution of product from Part B (574 mg, 1.01 mmol) in 40 mL of methanol, (the solution was not completely homogeneous), was treated with 70 mg of 10%

palladium on carbon catalyst and hydrogenated at 42 psig for 15h at room temperature. The catalyst was removed by filtration through diatomaceous earth and the filtrate concentrated in vacuo to give a white solid that was crystallized from chloroform, mp 123-127° C, FAB MS; M+Li+=412, 400 mg, 91%, that was used directly in the next step without further purification.

Part D: A mixture of 2(S)-methyl-3-methylsulfonyl propionic acid (112.3 mg, 0.675 mmol), N-hydroxybenzotriazole (159.1 mg, 1.04 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (147.8 mg, 0.77 mmol) was dissolved in 1.0 mL of dimethylformamide (DMF) and allowed to react for 30 min at 0°C. The amine from Part C (261.9 mg, 0.646 mmol) dissolved in 0.5 mL of DMF was added to the above mixture and stirred at room temperature for 16.5h. The solution was then poured into 75 mL of saturated aqueous NaHCO₃ and extracted with ethyl acetate: The ethyl acetate extracts were washed with 5% aqueous citric acid, saturated aqueous NaHCO₃, brine, dried over anhyd MgSO₄, filtered and concentrated to give a white foam, 326.3 mg. The material was purified by flash chromatography over silica gel eluting with ethyl acetate to provide 213.6 mg, 64% of pure product as a white foam, FAB MS; MH+=554.

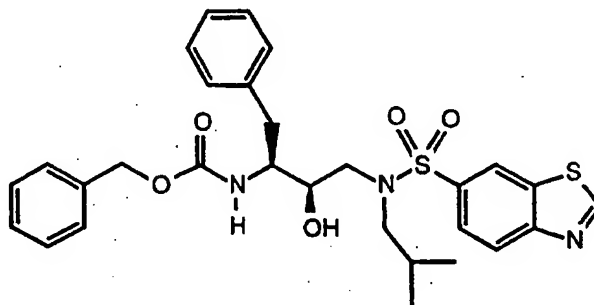
EXAMPLE 31



Preparation of Carbamic acid, 2R-hydroxy-3-[[[2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

- 5 Carbamic acid, 2R-hydroxy-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester 0.30 g (0.571 mmol) was added to a well mixed powder of anhydrous copper sulfate (1.20 g) and potassium thiocyanate (1.50 g) followed by dry
- 10 methanol (6 mL) and the resulting black-brown suspension was heated at reflux for 2 hrs. The reaction mixture was filtered and the filtrate was diluted with water (5 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon
- 15 concentration afforded a residue which was chromatographed (ethyl acetate:hexane 80:20) to afford 0.26 g (78%) of the desired compound as a solid.

EXAMPLE 32



Preparation of Carbamic acid, 2R-hydroxy-3-[[[2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester

25

Method 1:

- Carbamic acid, 2R-hydroxy-3-[[[2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester (0.25 g, 0.429 mmol) was
- 30 added to a solution of isoamylnitrite (0.116 mL, 0.858

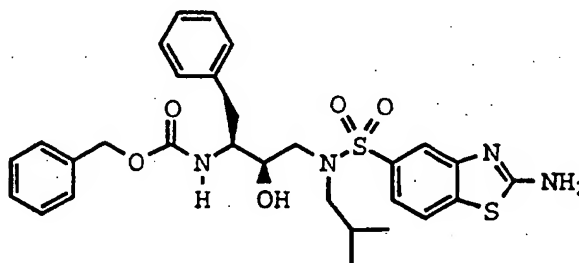
mmol) in dioxane (5 mL) and the mixture was heated at 85°C. After the cessation of evolution of nitrogen, the reaction mixture was concentrated and the residue was purified by chromatography (hexane:ethyl acetate 5:3) to afford 0.130 g (53%) of the desired product as a solid.

Method 2:

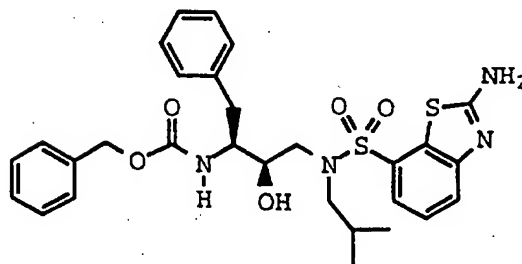
Crude benzothiazole-6-sulfonyl chloride in ethyl acetate (100 mL) was added to N-[3S-benzyloxycarbonyl amino-2R-hydroxy-4-phenyl]-N-isobutylamine (1.03 g, 2.78 mmol) followed by N-methylmorpholine (4 mL). After stirring at room temperature for 18 hr., the reaction mixture was diluted with ethyl acetate (100 mL), washed with citric acid (5%, 100 mL), sodium bicarbonate (saturated, 100 mL) and brine (100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was chromatographed (silica gel, ethyl acetate: hexane 1:1) to afford 0.340 g (23%) of desired product.

20

Example 33



and

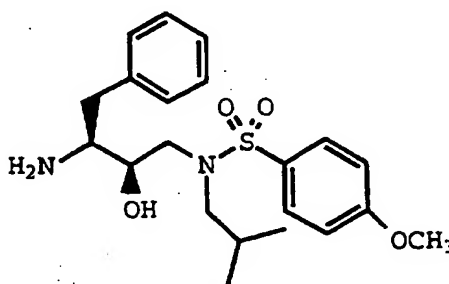


Preparation of Carbamic acid, 2R-hydroxy-3-[[[2-amino
benzothiazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-, phenylmethyl ester; and Carbamic
acid, 2R-hydroxy-3-[[[2-aminobenzothiazol-7-yl)sulfonyl]
5 (2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-,
phenylmethyl ester

The carbamic acid, 2R-hydroxy-3-[(3-aminophenylsulfonyl)
(2-methylpropyl)amino]-1S-(phenylmethyl)propyl-,
10 phenylmethyl ester 0.36 g (0.685 mmol) was added to a
well mixed powder of anhydrous copper sulfate (1.44 g)
and potassium thiocyanate (1.80 g) followed by dry
methanol (10 mL) and the resulting black-brown suspension
was heated at reflux for 2 hrs. The reaction mixture was
15 filtered and the filtrate was diluted with water (5 mL)
and heated at reflux. Ethanol was added to the reaction
mixture, cooled and filtered. The filtrate upon
concentration afforded a residue which was
chromatographed (ethyl acetate:hexane 1:1) to afford 0.18
20 g (45%) of the 7-isomer as a solid. Further elution of
the column with (ethyl acetate:hexane 3:2) afforded 0.80
g (20%) afforded the 5-isomer as a solid.

EXAMPLE 34

25



Preparation of 3S-amino-1-[(N-(2-methylpropyl)-N-(4-
methoxyphenyl)sulfonyl)amino]-4-phenyl-2R-butanol

30

Part A: N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol

To a solution of N-benzyloxycarbonyl-L-phenylalanine
5 chloromethyl ketone (75 g, 0.2 mol) in a mixture of 800
mL of methanol and 800 mL of tetrahydrofuran was added
sodium borohydride (13.17 g, 0.348 mol, 1.54 equiv.) over
100 min. The solution was stirred at room temperature
for 2 hours and then concentrated in vacuo. The residue
10 was dissolved in 1000 mL of ethyl acetate and washed with
1N KHSO₄, saturated aqueous NaHCO₃, saturated aqueous
NaCl, dried over anhydrous MgSO₄, filtered and
concentrated in vacuo to give an oil. The crude product
was dissolved in 1000 mL of hexanes at 60°C and allowed
15 to cool to room temperature where upon crystals formed
that were isolated by filtration and washed with copious
amounts of hexanes. This solid was then recrystallized
from hot ethyl acetate and hexanes to provide 32.3 g 43%
of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-
20 butanol, mp 150-151°C, FAB MS: MLi⁺ = 340.

Part B: 3(S)-[N-(benzyloxycarbonyl)amino]-1,2(S)-epoxy-4-phenylbutane

25 A solution of potassium hydroxide (6.52 g, 0.116 mol, 1.2
equiv.) in 970 mL of absolute ethanol was treated with N-
benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-
butanol (32.3 g, 0.097 mol). This solution was stirred
at room temperature for 15 minutes and then concentrated
30 in vacuo to give a white solid. The solid was dissolved
in dichloromethane and washed with water, dried over
anhyd MgSO₄, filtered and concentrated in vacuo to give
a white solid. The solid was crystallized from hexanes
and ethyl acetate to give 22.3 g, 77% of 3(S)-[N-
35 (benzyloxycarbonyl) amino]-1,2(S)-epoxy-4-phenylbutane,
mp 102-103°C, FAB MS: MH⁺ = 298.

Part C: N-[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine

A solution of N-benzylcarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenyl butane (50.0 g, 0.168 mol) and isobutylamine (246 g, 3.24 mol, 20 equivalents) in 650 mL of isopropyl alcohol was heated to reflux for 1.25 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 57.56 g, 92% of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]-N-isobutylamine, mp 108.0-109.5°C, MH⁺ m/z=371.

Part D: phenylmethyl [2(R)-hydroxy-3-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl)propyl]carbamate

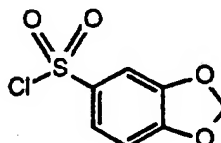
The amine from Part C (936.5 mg, 2.53 mmol) and triethylamine (2.88.5 mg, 2.85 mmol) was dissolved in 20 mL of dichloromethane and treated with 4-methoxybenzenesulfonyl chloride (461 mg, 2.61 mmol). The solution was stirred at room temperature for 16 hours and then concentrated in vacuo. The residue was dissolved in ethyl acetate and this solution was washed with 1N KHSO₄, saturated aqueous NaHCO₃, brine, dried over anhyd MgSO₄, filtered, and concentrated to give a clear oil 1.234 g. The oil was crystallized from a mixture of ether and hexanes, 729.3 mg, 56.5% mp 95-99°C, FAB MS: MH⁺ = 511.

Part E: 3S-amino-1-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-4-phenyl-2R-butanol

A solution of phenylmethyl [2(R)-hydroxy-3-[N-(2-methylpropyl)-N-(4-methoxyphenylsulfonyl)amino]-1S-(phenylmethyl) propyl carbamate (671.1 mg, 1.31 mmol) from Part D in 10 mL of methanol was hydrogenated over 50

mg of 10% palladium on carbon at 40 psig at room temperature for 15 hours. The catalyst was removed by filtration through diatomaceous earth and the filtrate concentrated to give a white foam, 474.5 mg, 96%, FAB MS:
5 $MH^+ = 377$.

EXAMPLE 35



10

Preparation of 1,3-benzodioxole-5-sulfonyl chloride

Method 1:

To a solution of 4.25 g of anhydrous N,N-dimethylformamide at 0°C under nitrogen was added 7.84g
15 of sulfonyl chloride, whereupon a solid formed. After stirring for 15 minutes, 6.45 g of 1,3-benzodioxole was added, and the mixture heated at 100°C for 2 hours. The reaction was cooled, poured into ice water, extracted
20 with methylene chloride, dried over magnesium sulfate, filtered and concentrated to give 7.32 g of crude material as a black oil. This was chromatographed on silica gel using 20% methylene chloride/hexane to afford
1.9 g of (1,3-benzodioxol-5-yl)sulfonyl chloride.

25

Method 2:

To a 22 liter round bottom flask fitted with a mechanical stirrer, a cooling condenser, a heating mantle and a pressure equalizing dropping funnel was added
30 sulfur trioxide DMF complex (2778g, 18.1 moles). Dichloroethane (4 liters) was then added and stirring initiated. 1,3-Benzodioxole (1905g, 15.6 moles) as then added through the dropping funnel over a five minute period. The temperature was then raised to 75°C and held
35 for 22 hours (NMR indicated that the reaction was done

after 9 hours.) The reaction was cooled to 26° and oxalyl chloride (2290g, 18.1 moles) was added at a rate so as to maintain the temperature below 40°C (1.5 hours). The mixture was heated to 67°C for 5 hours followed by

5 cooling to 16°C with an ice bath. The reaction was quenched with water (5 l) at a rate which kept the temperature below 20°C. After the addition of water was complete, the mixture was stirred for 10 minutes. The layers were separated and the organic layer was washed

10 again twice with water (5l). The organic layer was dried with magnesium sulfate (500g) and filtered to remove the drying agent. The solvent was removed under vacuum at 50°C. The resulting warm liquid was allowed to cool at which time a solid began to form. After one hour, the

15 solid was washed with hexane (400 mL), filtered and dried to provide the desired sulfonyl chloride (2823g). The hexane wash was concentrated and the resulting solid washed with 400 mL hexane to provide additional sulfonyl chloride (464g). The total yield was 3287g (95.5% based

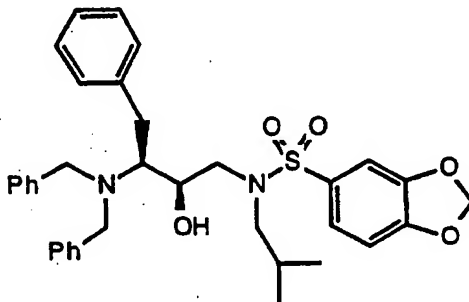
20 upon 1,3-benzodioxole).

Method 3:

1,4-benzodioxan-6-sulfonyl chloride was prepared according to the procedure disclosed in EP 583960,

25 incorporated herein by reference.

EXAMPLE 36



Preparation of 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-[bis(phenylmethyl)amino]-4-phenyl-2(R)-butanol

5 Method 1:

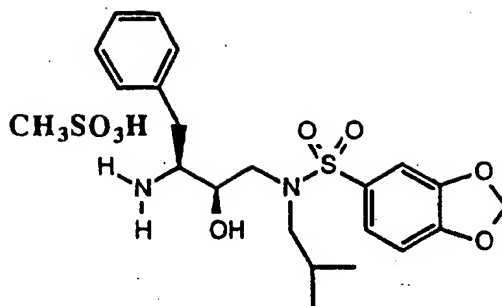
To a 5000 mL, 3-necked flask fitted with a mechanical stirrer was added N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine•oxalic acid salt (354.7 g, 0.7 mole) and
10 1,4-dioxane (2000 mL). A solution of potassium carbonate (241.9 g, 1.75 moles) in water (250 mL) was then added. The resultant heterogeneous mixture was stirred for 2 hours at room temperature followed by the addition of 1,3-benzodioxole-5-sulfonyl chloride (162.2 g, 0.735
15 mole) dissolved in 1,4-dioxane (250 mL) over 15 minutes. The reaction mixture was stirred at room temperature for 18 hours. Ethyl acetate (1000 mL) and water (500 mL) were charged to the reactor and stirring continued for another 1 hour. The aqueous layer was separated and
20 further extracted with ethyl acetate (200 mL). The combined ethyl acetate layers were washed with 25% brine solution (500 mL) and dried over anhydrous magnesium sulfate. After filtering and washing the magnesium sulfate with ethyl acetate (200 mL), the solvent in the
25 filtrate was removed under reduced pressure yielding the desired sulfonamide as an viscous yellow foamy oil (440.2g 105% yield). HPLC/MS (electrospray) (m/z 601 [M+H]⁺).

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EXAMPLE 37

Preparation of 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-amino-4-phenyl-2(R)-butanol•methanesulfonic acid salt

35



Method 1:

Crude 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-[bis(phenylmethyl)amino]-4-phenyl-2(R)-butanol (6.2g, 0.010 moles) was dissolved in methanol (40 mL). Methanesulfonic acid (0.969g, 0.010 moles) and water (5 mL) were then added to the solution. The mixture was placed in a 500 mL Parr hydrogenation bottle containing 20% Pd(OH)₂ on carbon (255 mg, 50% water content). The bottle was placed in the hydrogenator and purged 5 times with nitrogen and 5 times with hydrogen. The reaction was allowed to proceed at 35°C with 63 PSI hydrogen pressure for 18 hours. Additional catalyst (125 mg) was added and, after purging, the hydrogenation continued for an additional 20 hours. The mixture was filtered through celite which was washed with methanol (2 X 10 mL). Approximately one third of the methanol was removed under reduced pressure. The remaining methanol was removed by azeotropic distillation with toluene at 80 torr. Toluene was added in 15, 10, 10 and 10 mL portions. The product crystallized from the mixture and was filtered and washed twice with 10 mL portions of toluene. The solid was dried at room temperature at 1 torr for 6 hours to yield the amine salt (4.5 g, 84%). HPLC/MS (electrospray) was consistent with the desired product (m/z 421 [M+H]⁺).

Method 2:

Part A: N-[3(S)-[N,N-bis(phenylmethyl)amino]-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine•oxalic acid salt

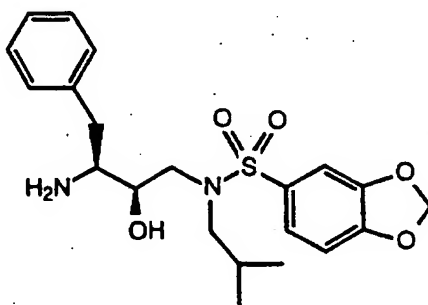
(2800g, 5.53 moles) and THF (4L) were added to a 22L round bottom flask fitted with a mechanical stirrer. Potassium carbonate (1921g, 13.9 moles) was dissolved in water (2.8L) and added to the THF slurry. The mixture was then stirred for one hour. 1,3-benzodioxole-5-sulfonyl chloride (1281g, 5.8 moles) was dissolved in THF (1.4L) and added to the reaction mixture over 25 minutes. An additional 200 mL of THF was used to rinse the addition funnel. The reaction was allowed to stir for 14 hours and then water (4 L) was added. This mixture was stirred for 30 minutes and the layers allowed to separate. The layers was removed and the aqueous layer washed twice with THF (500 mL). The combined THF layers were dried with magnesium sulfate (500 g) for one hour. This solution was then filtered to remove the drying agent and used in subsequent reactions.

Part B: To the THF solution of crude 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-[bis(phenylmethyl)amino]-4-phenyl-2(R)-butanol was added water (500 mL) followed by methane sulfonic acid (531g, 5.5 moles). The solution was stirred to insure complete mixing and added to a 5 gallon autoclave. Pearlman's catalyst (200g of 20% Pd(OH)₂ on C/ 50% water) was added to the autoclave with the aid of THF (500 mL). The reactor was purged four times with nitrogen and four times with hydrogen. The reactor was charged with 60 psig of hydrogen and stirring at 450 rpm started. After 16 hours, HPLC analysis indicated that a small amount of the mono-benzyl intermediate was still present. Additional catalyst (50g) was added and the reaction was allowed to run overnight. The solution was then filtered through celite (500g) to remove the catalyst and concentrated under vacuum in five portions. To each portion, toluene (500 mL) was added and removed under vacuum to azeotropically removed residual water. The resulting solid was divided into three portions and each washed with methyl t-butyl ether (2 L) and filtered. The

residual solvent was removed at room temperature in a vacuum oven at less than 1 torr to yield the 2714g of the expected salt.

If desired, the product can be further purified by the following procedure. A total of 500 mL of methanol and 170g of material from above was heated to reflux until it all dissolved. The solution was cooled, 200 mL of isopropanol added and then 1000-1300 mL of hexane, whereupon a white solid precipitated. After cooling to 0°C, this precipitate was collected and washed with hexane to afford 123g of the desired material. Through this procedure, the original material which was a 95:5 mixture of alcohol diastereomers was greater than 99:1 of the desired diastereomer.

EXAMPLE 38



20 Preparation of 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

Part A: Preparation of 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid phenylmethyl ester

To a solution of 3.19 g (8.6 mmol) of N-[3S-benzyloxy carbonylamino-2R-hydroxy-4-phenyl]-N-isobutylamine in 40mL of anhydrous methylene chloride, was added 0.87g of triethylamine. The solution was cooled to 0°C and 1.90g

of (1,3-benzodioxol-5-yl)sulfonyl chloride was added, stirred for 15 minutes at 0°C, then for 17 hours at room temperature. Ethyl acetate was added, washed with 5% citric acid, saturated sodium bicarbonate, brine, dried and concentrated to yield crude material. This was recrystallized from diethyl ether/hexane to afford 4.77 g of pure 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid phenylmethyl ester.

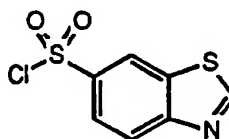
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Part B: Preparation of 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine

15 A solution of 4.11 g of carbamic acid, 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl-, phenylmethyl ester in 45 mL of tetrahydrofuran and 25 mL of methanol was hydrogenated over 1.1 g of 10% palladium-on-carbon under 50 psig of hydrogen for 16 hours. The catalyst was removed by filtration and the filtrate concentrated to afford 1.82g of the desired 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine.

25

EXAMPLE 39



30 Preparation of Benzothiazole-6-sulfonyl Chloride

Part A: Preparation of N-(4-Sulfonamidophenyl)thiourea

A mixture of sulfanilamide (86 g, 0.5 mole), ammonium thiocyanate (76.0 g, 0.5 mole) and dilute hydrochloric

35

acid (1.5 N, 1 L) was mechanically stirred and heated at reflux for 2 hr. About 200 mL of water was distilled off and concentration of the reaction mixture afforded a solid. The solid was filtered and was washed with cold water and air dried to afford 67.5 g (59%) of the desired product as a white powder.

Part B: Preparation of 2-Amino-6-sulfonamidobenzothiazole

10 Bromine (43.20 g, 0.27 mol) in chloroform (200 mL) was added over 1 hr. to a suspension of N-(4-sulfonamidophenyl)thiourea (27.72, 0.120 mol) in chloroform (800 mL). After the addition, the reaction mixture was heated at reflux for 4.5 hr. The chloroform
15 was removed in vacuo and the residue was repeatedly distilled with additional amounts of chloroform. The solid obtained was treated with water (600 mL) followed by ammonium hydroxide (to make it basic), then was heated at reflux for 1 hr. The cooled reaction mixture was
20 filtered, washed with water and air dried to afford 22.0g (80%) of the desired product as a white powder.

Part C: Preparation of Benzothiazole-6-sulfonic acid

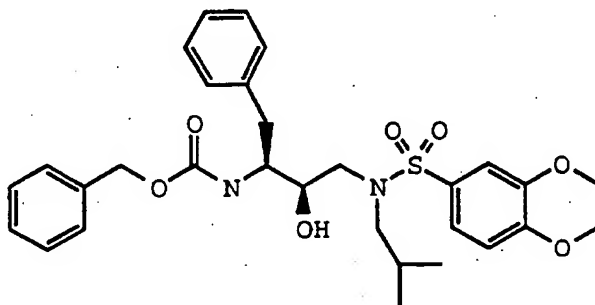
25 A suspension of 2-amino-6-sulfonamido-benzothiazole (10.0g, 43.67 mmol) in dioxane (300 mL) was heated at reflux. Isoamyl nitrite (24 mL) was added in two portions to the reaction mixture. Vigorous evolution of gas was observed (the reaction was conducted behind a shield as a
30 precaution) and after 2 hr., a red precipitate was deposited in the reaction vessel. The reaction mixture was filtered hot, and the solid was washed with dioxane and was dried. The solid was recrystallized from methanol-water. A small amount of a precipitate was
35 formed after 2 days. The precipitate was filtered off and the mother liquor was concentrated in vacuo to afford a pale red-orange solid (8.0 g, 85%) of pure product.

Part D: Preparation of 6-Chlorosulfonylbenzothiazole

Thionyl chloride (4 mL) was added to a suspension of the
5 benzothiazole-6-sulfonic acid (0.60 g, 2.79 mmol) in
dichloroethane (15 mL) and the reaction mixture was
heated at reflux and dimethylformamide (5 mL) was added
to the reaction mixture to yield a clear solution. After
1.5 hr. at reflux, the solvent was removed in vacuo and
10 excess HCl and thionyl chloride was chased by evaporation
with dichloroethane.

- EXAMPLE 40

15 Preparation of 2R-hydroxy-3-[[[1,4-benzodioxan-6-yl]
sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl
carbamic acid phenylmethyl ester



20

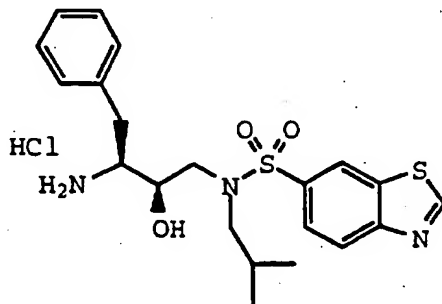
To a solution of the N-[3S-[(phenylmethoxycarbonyl)
amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)amine
(0.5 g, 1.35 mmol) in CH₂Cl₂ (5.0 mL) containing Et₃N
(0.35 mL, 2.5 mmol) was added 1,4-benzodioxan-6-sulfonyl
25 chloride (0.34 g, 1.45 mmol) and stirred at 0°C for 30
min. After stirring at room temperature for 1 hour, the
reaction mixture was diluted with CH₂Cl₂ (20 mL), washed
with cold 1N HCl (3 x 20 mL), water (2 x 20 mL), satd.
NaHCO₃ (2 x 20 mL) and water (3 x 20 mL), dried (Na₂SO₄)
30 and concentrated under reduced pressure. The resulting
residue was purified by flash chromatography using 35%
EtOAc in hexane to give the desired product as a white

amorphous solid which crystallized from MeOH as a white powder (0.65g, 84% yield): m. p. 82-84° C, HRMS-FAB : calcd for C₃₀H₃₇N₂O₇S 569.2321 (MH⁺), found 569.2323.

5

EXAMPLE 41

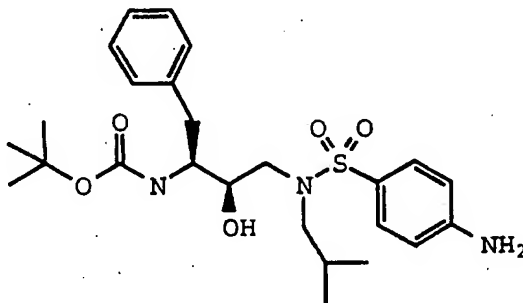
Preparation of [2R-hydroxy-3-[(benzothiazole-6-sulfonyl)-(2-methylpropyl)amino]-1S-(phenylmethyl)propylamine hydrochloride



10

Part A: Preparation of [2R-hydroxy-3-[(4-aminophenylsulfonyl)-(2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester

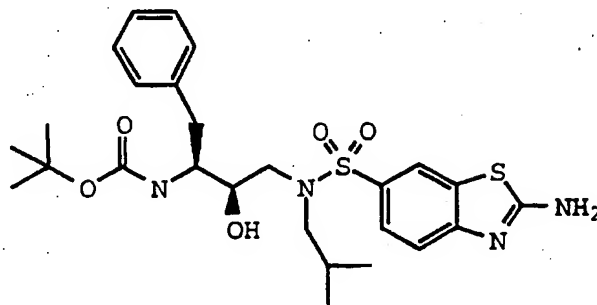
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A mixture of [2R-hydroxy-3-[(4-aminophenylsulfonyl)-(2-methylpropyl)-amino]-1S-(phenylmethyl)propylamine 3.7 g (9.45 mmol) and BOC-ON (2.33 g, 9.45 mmol) and triethylamine (0.954 g, 9.45 mmol) in tetrahydrofuran (60 mL) was stirred for 16 hours and concentrated in vacuo. The residue was dissolved in dichloromethane (200 mL), washed with sodium hydroxide (1N, 100 mL) and citric acid (5%, 100 mL), dried (MgSO₄), and concentrated to afford 1.18 g (94%) of the desired product as a white solid.

25

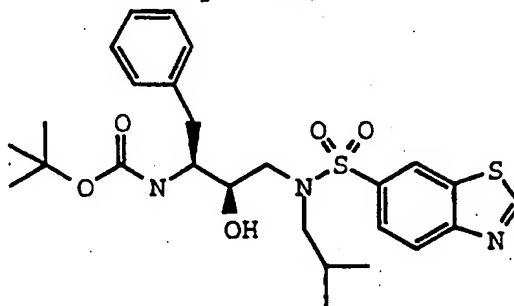
Part B: Preparation of [2R-Hydroxy-3-[[[2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester



5

The [2R-hydroxy-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester (1.12 g, 2.279 mmol) was added to a well
10 mixed powder of anhydrous copper sulfate (4.48 g) and potassium thiocyanate (5.60 g) followed by dry methanol (35 mL) and the resulting black-brown suspension was heated at reflux for 2 hours. The reaction mixture turned grey. The reaction mixture was filtered and the
15 filtrate was diluted with water (50 mL) and heated at reflux. Ethanol was added to the reaction mixture, cooled and filtered. The filtrate upon concentration afforded a residue which was chromatographed (ethyl acetate:methanol 90:10) to afford 0.80 g (78%) of the
20 deprotected compound as a solid. This was directly reprotected via the following procedure; (2.25 g, 5.005 mmol) BOC-ON (1.24 g), and triethylamine (0.505 g, 5.005 mmol) in tetrahydrofuran (20 mL) was stirred at room temperature for 18 hours. The reaction mixture was
25 concentrated and the residue was dissolved in dichloromethane (200 mL) and was washed with sodium hydroxide (1N, 100 mL) and citric acid (5%, 100 mL) dried (MgSO₄) and concentrated to afford a residue which was chromatographed (ethyl acetate:hexane 3:1) to afford 1.8
30 g (65%) of the desired product as a solid.

Part C: Preparation of [2R-hydroxy-3-[[[(benzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester

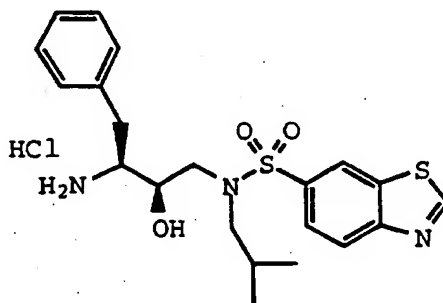


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[2R-Hydroxy-3-[[[(2-aminobenzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester (1.80 g, 3.2755 mmol) was added to a solution of isoamyl nitrite (0.88 mL) in dioxane (20 mL) and the mixture was heated at 85°C. After the cessation of evolution of nitrogen, the reaction mixture was concentrated and the residue was purified by chromatography (hexane:ethyl acetate 1:1) to afford 1.25 g (78%) of the desired product as a solid.

15

Part D: Preparation of [2R-hydroxy-3-[[[(benzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine·hydrochloride.



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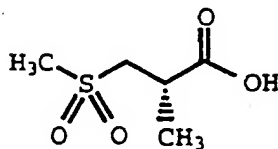
[2R-hydroxy-3-[[[(benzothiazol-6-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamic acid t-butyl ester (1.25 g, 2.3385 mmol) was added dioxane/HCl (4N, 10 mL) and was stirred at room temperature for 2 hours and concentrated. Excess HCl was chased with

25

toluene to afford 1.0 g (quantitative yield) of the desired product.

EXAMPLE 42

5



Preparation of 2(S)-methyl-3-(methylsulfonyl)propionic Acid

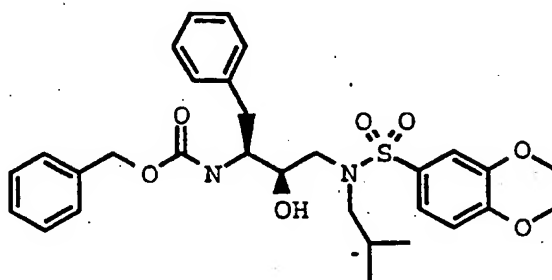
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Part A: To a solution of 200 g (1.23 mol) of D-(-)-3-acetyl-b-mercaptoisobutyric acid in 1.0 L of methanol, was added 161.0 g (2.47 mol) of potassium hydroxide dissolved in 500 mL of methanol while maintaining the temperature below 10°C while cooling with an ice bath. After stirring an additional 20 minutes, 117 mL (156 g, 1.23 mol) of dimethyl sulfate was added while maintaining the temperature below 20°C. The ice bath was removed and the mixture stirred for an additional 60 minutes. The salts were removed by filtration, the solvents removed under reduced pressure and ethyl acetate added. After separating the aqueous layer, it was acidified with concentrated hydrochloric acid, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 164 g (99%) of the desired 2S-methyl-3-(methylthio)propionic acid, m/e = 133 (M-H).

Part B: To a solution of 10.0 g (74.6 mmol) of 2S-methyl-3-(methylthio)propionic acid in 150 mL of acetone and 30 mL of water, cooled to 18 C in an ice bath, was added 161.8 g (263 mmol) of Oxone. After approximately half of material had been added, the temperature rose to 24°C, the addition was stopped, temperature lowered to 18°C, then addition continued. After stirring at 15-20°C for 15 minutes, the bath was removed and the reaction

stirred at room temperature for 1 hour. The solids were filtered and washed with acetone, the filtrate concentrated to approximately 40 mL and the residue dissolved in 200 mL of ethyl acetate. The ethyl acetate layer was dried with anhydrous magnesium sulfate, filtered and concentrated to afford 11.4 g of an oil. This was dissolved in a minimum of ethyl acetate and hexane added to cause a precipitate to form. This was collected to afford 6.95 g of the desired product, m/e = 167 (M+H).

EXAMPLE 43



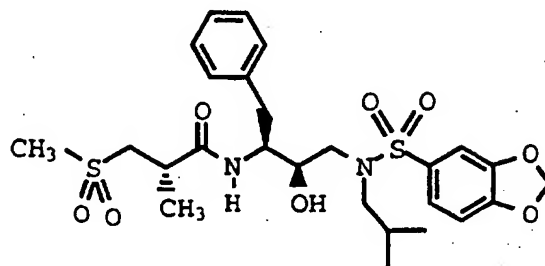
15

Preparation of 1-[(2-methylpropyl)][(1,4-benzodioxane-6-yl)sulfonyl]amino]-3S-[(phenylmethoxycarbonyl)amino]-4-phenylbutan-2R-ol

To a solution of the N-[3S-[(phenylmethoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)amine (0.5 g, 1.35 mmol) in CH₂Cl₂ (5.0 mL) containing Et₃N (0.35 mL, 2.5 mmol) was added 1,4-benzodioxan-6-sulfonyl chloride (0.34 g, 1.45 mmol) (prepared according to the literature procedure in EP 583960 A2, 1994) and stirred at 0°C for 30 min. After stirring at room temperature for 1h, the reaction mixture was diluted with CH₂Cl₂ (20 mL), washed with cold 1N HCl (3 x 20 mL), water (2 x 20 mL), satd. NaHCO₃ (2 x 20 mL), water (3 x 20 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using 35% EtOAc in hexane to give the desired 1,4-

benzodioxan-sulfonamide as a white amorphous solid which crystallized from MeOH as a white powder (0.65g, 84%): m.p. 82-84°C, HRMS-FAB : calcd for C₃₀H₃₇N₂O₇S 569.2321 (MH⁺), found 569.2323.

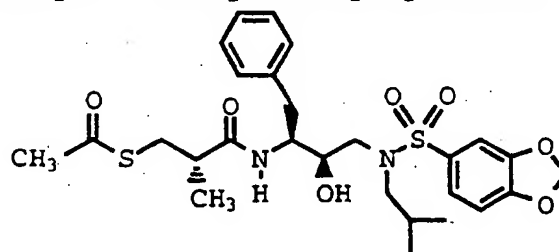
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EXAMPLE 44

10 Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(methylsulfonyl)propanamide

Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(acetylthio)propanamide

15



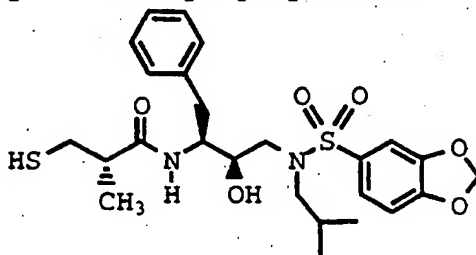
N-Hydroxybenzotriazole (1.79 g, 11.6 mmol) was added to solution D-(-)-S-acetyl-β-mercaptoisobutyric acid (1.26 g, 7.8 mmol) in 15 mL of dry dimethylformamide and cooled in an ice bath. To the cooled solution, was added EDC (1.64 g, 8.5 mmol) and stirred for 30 minutes. To this was added (3.27 g, 7.8 mmol) of 2R-hydroxy-3-[[[(1,3-benzodioxol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine and this was stirred 16 hours with warming to room temperature. The solvent was removed and the residue partitioned between ethyl acetate

20

25

and 5% aqueous potassium hydrogen sulfate. The organic layer was washed with saturated sodium bicarbonate, and brine, dried over magnesium sulfate filtered and concentrated to yield 4.4 grams of a crude oil, mass spectrum, $m/z=571.8$ ($M+Li$); HRMS: calcd for $C_{27}H_{36}N_2O_7S_2$ 565.2042, found 565.2028.

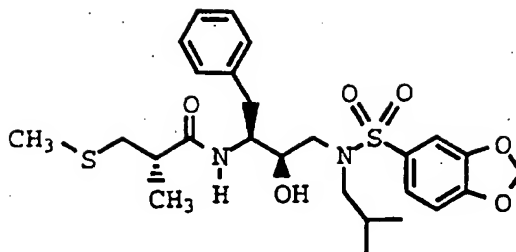
Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-mercaptopropanamide



A solution of 4.29 g, (7.8 mmol) of S-acetyl compound from part A dissolved in 100 mL of dry methanol was cooled in an ice bath. Anhydrous ammonia was bubbled into the solution for one minute. The solution was stoppered and stirred to room temperature over 5 hours. The contents were concentrated on a rotary evaporator, and the residue was dissolved in ethyl acetate. The organic solution was washed with water, and brine, dried over magnesium sulfate, filtered and concentrated to yield 3.9 grams of the free mercaptan which was used without purification; mass spectrum, $m/z = 529.8$ ($M+Li$); HRMS: calcd for $C_{25}H_{34}N_2O_6S_2$ 523.1937, found 523.1942.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-(methylthio)propanamide

117



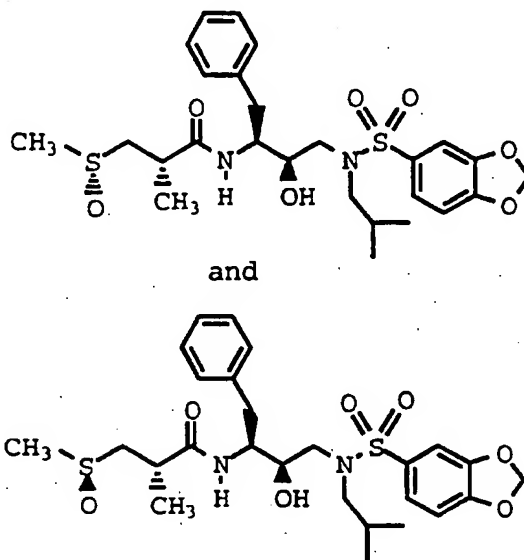
A solution of 1.65 g, (3.15 mmol) of the mercaptan from Part B in 25 mL of tetrahydrofuran was cooled in an ice bath. To this cooled solution was added 0.52 g, 3.52 mmol) of DBU followed by 0.22 mL, (3.5 mmol) of methyl iodide and the ice bath was removed after 5 minutes. After several hours at room temperature the contents were concentrated on a rotary evaporator, and the residue was dissolved in ethyl acetate. The organics were washed with potassium hydrogen sulfate, sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated to yield 1.48 g of a crude white foam.

Part D: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-(methylsulfonyl)propanamide

To a solution of 440 mg, (0.8 mmol) of thiomethylether from part C above dissolved in 10 mL of methanol, was added 1.52g, (24.0 mmol) of oxone followed by 10 mL of water. The suspension was stirred at room temperature for four hours. The mixture was concentrated on a rototry evaporator, diluted with 50 mL of water and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate, dried over magnesium sulfate, filtered and concentrated to yield 390 mg of crude sulfone. Purification by flash chromatography using 1:1 ethyl acetate ; hexane as the eluant yielded 330 mg of the desired compound; mass spectrum, m/z=575.4 (M+Li).

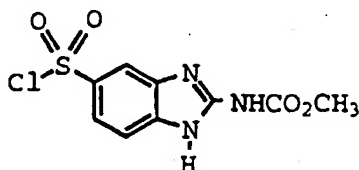
EXAMPLE 45

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(methylsulfinyl)propanamide



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To a solution of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(methylthio)propanamide 1.04 g (1.94 mmol) in 10 mL of glacial acetic acid was added 220 mg (1.94 mmol) of 30% hydrogen peroxide with stirring. After one hour the reaction was stopped by diluting with water and neutralization by the careful addition of saturated sodium bicarbonate. The resulting aqueous suspension was extracted with ethyl acetate, and the organics were washed with 5% aqueous potassium hydrogen sulfate. The ethyl acetate layer was dried over magnesium sulfate, filtered, and concentrated to yield a mixture of diastereomeric sulfoxides. Separation of the two diastereomers by careful flash chromatography yielded 250 mg of fast moving isomer 1, and 250 mg of slow moving isomer 2, and 400 mg of the mixture, mass spectrum, $m/z=559.3$ ($M+Li$) isomer 1, and $m/z = 559.3$ isomer 2.

EXAMPLE 46Preparation of 5-chlorosulfonyl-2-carbomethoxyamino-benzimidazole

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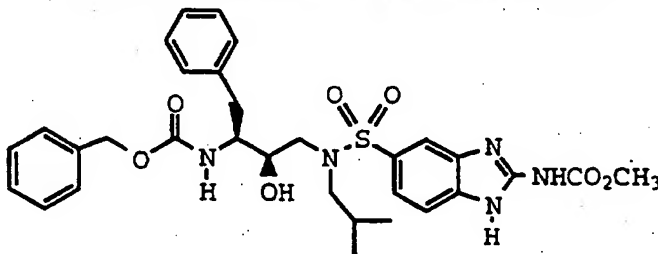
A solution of 2-carbomethoxyamino-benzimidazole (5.0 g, 0.026 mole) in chlorosulfonic acid (35.00 mL) was stirred at 0°C for 30 minutes and at room temperature for 3 hours. The resulting dark colored reaction mixture was poured into an ice-water mixture (200 mL), and stirred at room temperature for 30 minutes. The resulting precipitate was filtered and washed with cold water (500 mL). The solid was dried overnight under high vacuum in a desiccator over NaOH pellets to give 5-chlorosulfonyl-2-carbomethoxyamino-benzimidazole (5.9 g, 78%) as a grey powder. ¹H NMR (DMSO-*d*₆) δ: 3.89 (s, 3H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.88 (s, 1H). (German Patent DE 3826036)

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EXAMPLE 47

Preparation of N-[2R-hydroxy-3-[N¹-(2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl]-N¹-(2-methylpropyl)amino]-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester

25

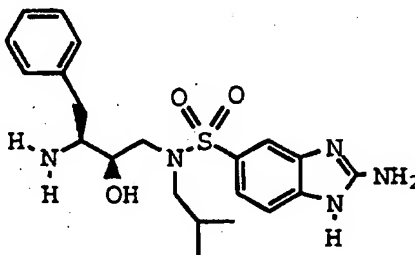


To a cold solution of N-[3S-[(phenylmethoxycarbonyl)amino]-2R-hydroxy-4-phenylbutyl]-N-(2-methylpropyl)amine

(5.0 g, 13.5 mmol) in dichloromethane (70 mL) was added triethylamine (5.95 g, 54.0 mmol) followed by the addition of 5-chlorosulfonyl-2-carbomethoxyamino-benzimidazole (4.29 g, 14.85 mmol) in small portions as a solid. The reaction mixture was stirred at 0°C for 30 minutes and at room temperature for 2.5 hours when reaction of the amino alcohol was complete. The mixture was cooled and filtered, and the filtrate was concentrated. The resulting residue was dissolved in EtOAc (200mL), washed successively with cold 5% citric acid (3 x 50 mL), saturated aqueous sodium bicarbonate (3 x 50 mL) and water (3 x 100 mL), then dried (Na₂SO₄), concentrated and dried under vacuum. The residue was triturated with methanol, cooled, filtered, washed with MeOH-EtOAc (1:1, v/v) and dried in a desiccator to give pure N-[2R-hydroxy-3-[[[(2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)-amino]-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester (6.02 g, 72 %) as a light brown powder: FABMS: m/z = 630 (M+Li); HRMS: calcd. for C₃₁H₃₈N₅O₇S (M+H) 624.2492, found 624.2488.

EXAMPLE 48

Preparation of 2R-hydroxy-3-[[[(2-amino-benzimidazol-5-yl)sulfonyl](2-methyl-propyl)amino]-1S-(phenylmethyl)propylamine



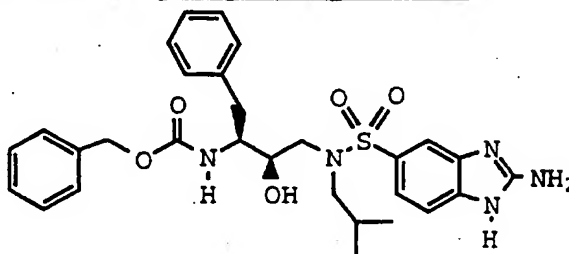
A solution of N-[2R-hydroxy-3-[[[(2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester (0.36 g, 0.58 mmol) in 2.5 N methanolic KOH (2.00 mL) was

heated at 70°C under a nitrogen atmosphere for 3 hours. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated. The resulting residue was purified by reverse-phase HPLC using a 10-90% CH₃CN/H₂O gradient (30 min) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to give pure 2R-hydroxy-3-[[[(2-amino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenyl-methyl)propylamine (0.22 g, 58%) as a white powder: FAB-MS *m/z* = 432 (M+H); HRMS: calcd. for C₂₁H₃₀N₅O₃S (M+H) 432.2069, found 432.2071.

EXAMPLE 49

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Preparation of N-[2R-hydroxy-3-[[[(2-amino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)-aminol-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester



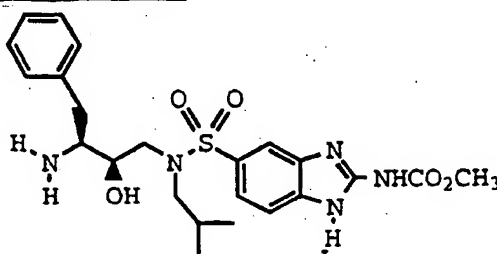
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To a solution of 2R-hydroxy-3-[[[(2-amino-benzimidazol-5-yl)sulfonyl](2-methyl-propyl)amino]-1S-(phenylmethyl)propylamine (0.22 g, 0.33 mmol) in THF (3.00 mL), triethylamine (0.11 g, 1.1 mmol) and benzyloxycarbonyl succinimide (0.09 g, 0.36 mmol) were added, and the reaction mixture was stirred at room temperature for 16 hours. The solution was concentrated, and the residue was partitioned between EtOAc (15 mL) and saturated aqueous sodium bicarbonate. The organic phase was washed with brine, dried (Na₂SO₄), and concentrated. The resulting residue was purified by reverse-phase HPLC using a 10-90% CH₃CN/H₂O gradient (30 min) at a flow rate

of 70 mL/min. The appropriate fractions were combined and freeze dried to give pure N-[2R-hydroxy-3-[[[2-amino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester (0.12 g, 61%) as a white powder: FAB-MS m/z = 566 (M+H); HRMS: calcd. for $C_{29}H_{36}N_5O_5S$ 566.2437 (M+H), found 566.2434.

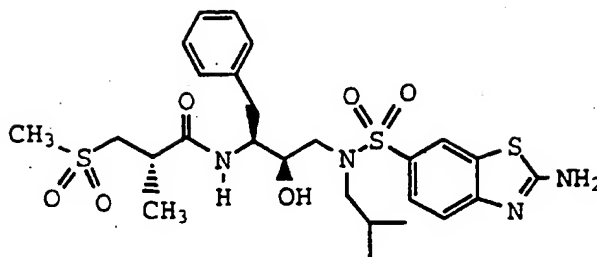
EXAMPLE 50

Preparation of 2R-hydroxy-3-[[[2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine



15

A solution of N-[2R-hydroxy-3-[[[2-carbomethoxyamino-benzimidazole-5-yl)sulfonyl](2-methylpropyl)-amino]-1S-(phenylmethyl)propyl]carbamic acid phenylmethyl ester (2.5 g, 0.4 mmol) in MeOH (10 mL) and THF (50 mL) was hydrogenated in the presence of 10% Pd/C (1.2 g) at room temperature at 60 psi for 16 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was triturated with ether and filtered. The solid substance thus obtained was washed with ether and dried in vacuo to afford pure 2R-hydroxy-3-[[[2-carbomethoxyamino-benzimidazol-5-yl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylamine (1.5 g, 77%) as an off white powder: R_t = 12.8 min; FAB-MS m/z = 490 (M+H); HRMS: calcd. for $C_{23}H_{32}N_5O_5S$ 490.2124 (M+H), found 490.2142.

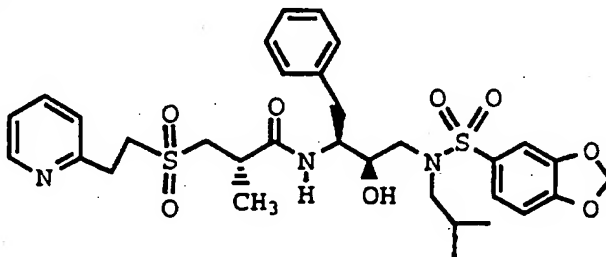
EXAMPLE 51

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(2-
 5 aminobenzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-(methylsulfonyl)propanamide

To a solution of 2-(S)-methyl-3-methylsulfonyl propionic
 acid (0.249 g, 1.5 mmol) in 5 mL of dry
 10 dimethylformamide, was added 1.5 equivalents of N-
 hydroxy-benzotriazole, and the solution was cooled in an
 ice bath. To this cooled solution was added EDC (0.200g,
 1.5 mmol), and the solution was stirred for 30 minutes.
 To this was added 2R-hydroxy-3-[[2-aminobenzothiazol-6-
 15 yl)sulfonyl](2-methyl-propyl)amino]-1S-(phenylmethyl)
 propylamine (0.673 g, 1.5mmol); and the reaction stirred
 for 16 hours. The contents were concentrated in vacuo
 and the residue was dissolved in ethyl acetate, washed
 with 5% potassium hydrogen sulfate, saturated sodium
 20 bicarbonate, and brine, dried over magnesium sulfate,
 filtered and concentrated to yield a crude oil.
 Purification by flash column chromatography on silica gel
 using an eluant of 1:1:0.1 ethyl acetate: hexane:methanol
 yielded pure N-[2R-hydroxy-3-[(2-methylpropyl) [(2-amino-
 25 benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)
 propyl]-2S-methyl-3-(methyl-sulfonyl)propanamide; FAB-MS:
 $m/z = 598.6$ (M+H).

EXAMPLE 52

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-(2-pyridyl)ethylsulfonyl)-propanamide



Part A: Preparation of 2-(2-chloroethyl)pyridine.
hydrochloride

2-(2-hydroxyethyl)pyridine (5 g, 41 mmol) was dissolved in 10 mL of 1,2-dichloroethane, and thionyl chloride (9.67 g, 81 mmol) was added slowly at room temperature. The reaction mixture was stirred for one hour at room temperature and was then concentrated at reduced pressure. Methylene chloride (20 mL) was twice added to the concentrated residue and then removed under reduced pressure. The resulting concentrated residue was dried in vacuo to give 7.17 g (98.5 %) of 2-(2-chloroethyl)pyridine·hydrochloride as a yellow solid: HRMS: calcd for C₇H₈N₁Cl₁ 142.0424, found 142.0400.

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-(2-pyridyl)ethylthio)propanamide

2-(2-chloroethyl)pyridine·hydrochloride (0.20 g, 1.15 mmol), potassium bromide (0.28 g, 2.39 mmol) and a catalytic amount of 18 crown-6 were dissolved in 2.5 mL of N,N-dimethylacetamide (DMA) and stirred at room temperature for two hours. N-[2R-hydroxy-3-[(2-

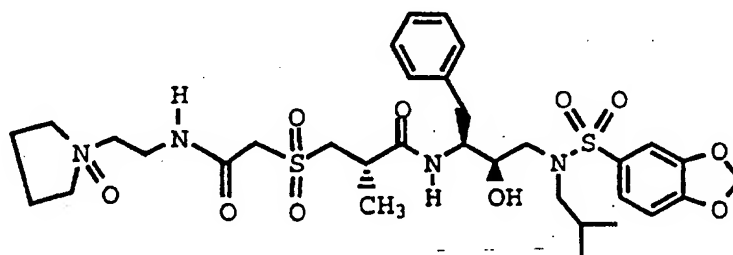
methylethylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.5 g, 0.96 mmol) and 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU, 0.44 g, 2.87 mmol) were dissolved in 2.5 mL of DMA and added to this solution. The reaction mixture was stirred at room temperature for 24 hours, then the DMA was removed under vacuum. The residue was brought up in 150 mL of dichloromethane, and the organic solution was washed with 5 % aqueous NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 50:50 (v/v) ethylacetate:hexane to give 0.31 g (51.7 %) of the desired sulfide product as a yellow gum: HRMS: calcd for C₃₂H₄₁N₃O₆S₂ 628.2515, found 628.2525.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylethylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-(2-pyridyl)ethylsulfonyl)propanamide

The sulfide product from Part B (0.25 g, 0.40 mmol) was dissolved in 9 mL of methanol. Then oxone (0.74 g, 1.20 mmol) and 1.5 mL of water were added to the methanolic solution. The reaction mixture was stirred for 4.5 hours at room temperature. The reaction mixture was cooled in an ice bath, and 5 % aqueous NaHCO₃ (10 mL) was added. The methanol was removed in vacuo, and the residue was brought up in 100 mL of dichloromethane. The dichloromethane solution was washed with (2 x 50 mL) 5% NaHCO₃, brine (2 x 50 mL), dried over MgSO₄, filtered, and the filtered was concentrated, and dried in vacuo to give 0.12 g (45.6 %) of the desired sulfone as a white solid: HRMS: calcd for C₃₂H₄₁N₃O₈S₂ 660.2413, found 660.2421.

EXAMPLE 53

- Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[N-(2-(1-oxopyrrolidin-1-yl)ethyl)aminocarbonyl]methyl]sulfonyl]propanamide



- 10 Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[N-(2-(1-pyrrolidinyl)ethyl) aminocarbonyl]methyl]thio]propanamide
- 15 1-(2-aminoethyl)pyrrolidine (0.11 g, 0.95 mmol), chloroacetic anhydride (0.16 g, 0.95 mmol) and triethylamine (96 mg, 0.95 mmol) were combined with 5 mL of methylene chloride at 5°C in a 25 mL round bottom flask. The reaction mixture was warmed up to room
- 20 temperature and then was stirred at room temperature for one hour. The reaction mixture was then cooled in an ice-water bath to 5°C. N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-mercaptopropanamide (0.50 g, 0.95
- 25 mmol) and triethylamine (96 mg, 0.95 mmol) were dissolved in 5 mL of methylene chloride and added to the above solution such that the temperature did not rise above 5°C. The reaction mixture was warmed to room temperature and stirred at room temperature for two hours.
- 30 Triethylamine (0.20 g, 1.90 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with 100

mL of methylene chloride. The organic solution was washed with saturated aqueous NaHCO₃ (2 x 50 mL), brine (2 x 50 mL) and was dried over MgSO₄, filtered and concentrated at reduced pressure. The resulting residue was purified by flash chromatography on silica gel eluting with 10% methanol in methylene chloride to give 0.28 g (43.5%) of the desired sulfide product as a pale yellow solid: HRMS: calcd for C₃₃H₄₈N₄O₇S₂ 677.3043, found 677.3051.

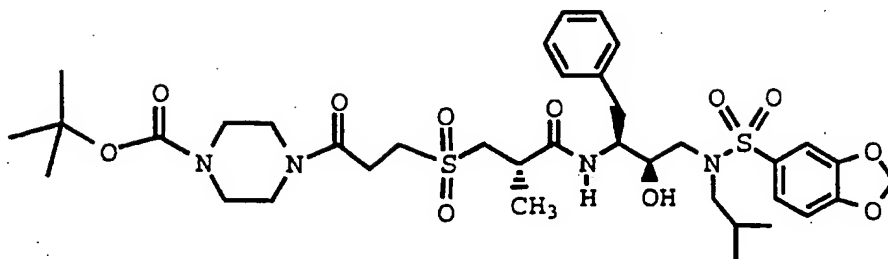
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Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[N-(2-(1-oxopyrrolidin-1-yl)ethyl) aminocarbonyl]methyl]sulfonyl]propanamide

15

The sulfide product from Part B (0.26 g, 0.38 mmol) was dissolved in 10 mL of methanol. Then oxone (0.71 g, 1.15 mmol) and 2 mL of water were added to the methanolic solution. The reaction mixture was stirred for twenty hours at room temperature, and the methanol was removed under reduced pressure. The concentrated residue was brought up in 100 mL of methylene chloride. The organic solution was washed with saturated aqueous NaHCO₃ (2 x 50 mL), brine (2 x 50 mL), dried over MgSO₄, filtered and concentrated at reduced pressure. The concentrated residue was purified by flash chromatography on silica gel eluting with a 15% to 25% methanol gradient in methylene chloride to give 0.1 g of the desired sulfone as a pale yellow solid. The crude product was purified by preparative reverse phase HPLC (30-90 % acetonitrile in water containing 0.1 % trifluoroacetic acid) to give 35 mg (12.6 %) of the desired pure sulfone product as a pale yellow solid: HRMS: calcd for C₃₃H₄₈N₄O₁₀S₂ 725.2890, found 725.2902.

35

EXAMPLE 54

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(4-(t-butoxycarbonyl)piperazin-1-yl)carbonyl]ethyl]sulfonyl]propanamide

Part A: Preparation of 1-(3-chloropropionyl)-4-(t-butoxycarbonyl)piperazine

4-(t-butoxycarbonyl)piperazine (3 g, 16 mmol) was suspended in 10 mL of methylene chloride and cooled in an ice/water bath. 3-Chloropropionyl chloride (2.04 g, 16 mmol) was dissolved in 10 mL of methylene chloride and added slowly, while maintaining the internal temperature below 5°C. Triethylamine (1.63 g, 16 mmol) was then added to the cold (5°C) solution. The solution was slowly warmed to room temperature and then stirred at room temperature overnight. The reaction mixture was diluted with 150 mL of methylene chloride and washed with 5% aqueous NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered, concentrated and dried under vacuum to give 3.71 g of crude product. The crude material was purified by flash chromatography on silica gel eluting with ethyl acetate to give 1.85 g (41.8%) of 1-(3-chloropropionyl)-4-(t-butoxycarbonyl)piperazine as a pale yellow solid. ¹H NMR (300 MHz/CDCl₃): δ 1.47 (s, 9H), 2.82 (t, 2H, J = 6.95 Hz), 3.40-3.46 (m, 6H), 3.60-3.63 (m, 2H), 3.84 (t, 2H, J = 6.95 Hz); mass spectrum, m/z = 283.1 (M+Li); high-resolution FAB-MS calcd for C₁₂H₂₁N₂O₃Cl 276.1240 (M+), found 276.1227.

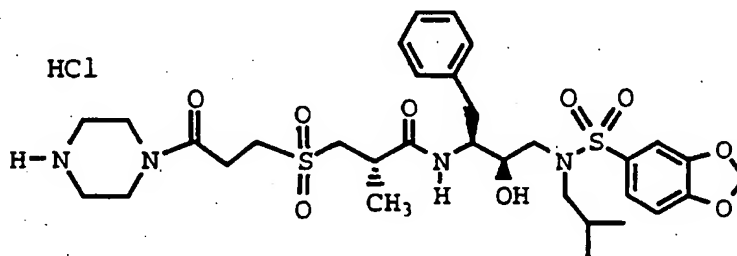
Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[[2-(4-(t-butoxycarbonyl)piperazin-1-
5 ylcarbonyl)ethyl]thio]propanamide

1-(3-Chloropropionyl)-4-(t-butoxycarbonyl)piperazine
(0.38 g, 1.38 mmol), potassium bromide (0.2 g, 1.72 mmol)
and a catalytic amount of 18-crown-6 were dissolved in 5
10 mL of N,N-dimethylacetamide (DMA) and stirred at room
temperature for 2.5 hours. N-[2R-hydroxy-3-[(2-
methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-
(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide
(0.6 g, 1.15 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene
15 (0.19 g, 1.26 mmol) were dissolved in 5 mL of DMA and
then added to the reaction mixture. The reaction mixture
was stirred at room temperature for 18 hours, and then
the DMA was removed under vacuum. The residue was
brought up in 150 mL of dichloromethane and washed with
20 5% aqueous NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried
over MgSO₄, filtered and concentrated. The crude
material was purified by flash chromatography on silica
gel eluting with 50:50 (v/v) ethyl acetate:hexane to give
0.34 g (38.7 %) of the desired sulfide as a white foaming
25 solid: HRMS: calcd for C₃₇H₅₄N₄O₉S₂ 763.3410, found
763.3437.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
30 propyl]-2S-methyl-3-[[2-(4-(t-butoxycarbonyl)piperazin-1-
ylcarbonyl)ethyl]sulfonyl]propanamide

The sulfide product from Part B (0.3 g, 0.39 mmol) was
dissolved in 15 mL of methanol. Then oxone (0.72 g, 1.18
35 mmol) and 3 mL of water were added to the methanolic
solution. The reaction mixture was stirred for 5 hours
at room temperature, and the methanol was removed under

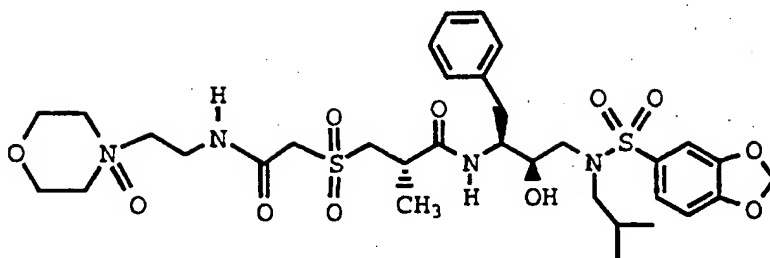
vacuum. The resulting residue was brought up in 100 mL of dichloromethane. The dichloromethane solution was washed with (2 x 50 mL) water, brine (2 x 50 mL), dried over MgSO₄, filtered, and concentrated in vacuo to give
 5 0.26 g (83.9%) of the desired sulfone as a white solid: HRMS: calcd for C₃₇H₅₄N₄O₁₁S₂ 795.3309, found 795.3312.

EXAMPLE 55

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Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(piperazin-1-ylcarbonyl)ethyl]sulfonyl]propanamide hydrochloride
 15

N-[2R-Hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(4-(t-butoxycarbonyl)piperazin-1-ylcarbonyl)ethyl]sulfonyl]propanamide (0.2 g, 0.25 mmol) was treated with
 20 5 mL of 4 N HCl in dioxane under nitrogen. The reaction mixture was stirred for 3 hours at room temperature, then the mixture was concentrated under reduced pressure. Methylene chloride (several mL) was added to the
 25 concentrated residue and then removed under reduced pressure. The resulting residue was dried in vacuo to give 0.21 g of the desired deprotected piperazine sulfone as a white solid. This solid was recrystallized from ethyl acetate and ether to produce 80 mg (44.4 %) of pure
 30 product as a white solid: HRMS: calcd for C₃₂H₄₆N₄O₉S₂ 695.2784, found 695.2812.

EXAMPLE 56

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonylaminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[(2-(4-oxomorpholin-4-yl)ethyl)aminocarbonyl]methyl]sulfonyl]propanamide

Part A: Preparation of N-(2-chloroacetyl)-2-(4-morpholinyl)ethylamine

Chloroacetyl chloride (1.73 g, 15 mmol) was dissolved in 4 mL of dichloromethane and cooled to 5°C in an ice-water bath. 4-(2-Aminoethyl)morpholine (2 g, 15 mmol) was dissolved in 4 mL of dichloromethane containing triethylamine (3.03 g, 30 mmol) which was then added to this cold solution at 5°C. A solid precipitate formed immediately after the triethylamine was added. The reaction mixture was stirred for 3 hours at room temperature. The reaction mixture was diluted with 100 mL of dichloromethane and 20 mL of water. The organic solution was washed with 5% aqueous NaHCO₃ (2 x 50 mL), brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was dried in vacuo to give 2.57 g (83.7 %) of N-(2-chloroacetyl)-2-(4-morpholinyl)ethylamine as a yellow solid. ¹H NMR (300 MHz / CDCl₃): δ 2.48-2.55 (m, 6H), 3.38 (dd, 2H, J = 5.63 Hz), 3.71 (t, 4H, J = 4.53 Hz), 4.04 (s, 2H); mass spectrum, m/z = 207.1 (M+H); HRMS calcd for C₈H₁₅N₂O₂Cl₁ 206.0822, found 206.0814.

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[(2-(4-oxomorpholin-4-yl)ethyl) aminocarbonyl)methyl]thio]propanamide

5

To an ice-cold solution of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.5 g, 0.96 mmol) in 8 mL of dichloromethane was added
10 N-(2-chloroacetyl)-2-(4-morpholinyl)ethylamine (0.2 g, 0.96 mmol) in 8 mL of dichloromethane containing triethylamine (0.14 g, 1.43 mmol). The reaction mixture was stirred for 1 hour at 5°C then warmed up to room temperature and stirred for 60 hours at room temperature.
15 The reaction mixture was diluted with 150 mL of dichloromethane. The organic solution was washed with 5% aqueous NaHCO₃ (2 x 100 mL), water (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered and concentrated under vacuum. The resulting residue was purified by
20 flash chromatography on silica gel eluting with a 0-6% methanol gradient in dichloromethane to give 0.33 g (49.8%) of the desired sulfide product as a white solid: HRMS calcd for C₃₃H₄₈N₄O₈S₂ 693.2992, found 693.2997.

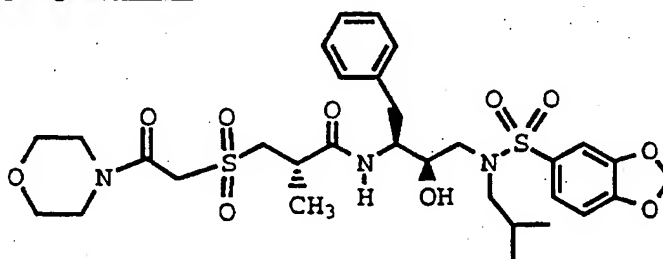
25 Part C: N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[(2-(4-oxomorpholin-4-yl)ethyl) aminocarbonyl)methyl]sulfonyl]propanamide

30 To a solution of the sulfide product from Part B (0.25 g, 0.36 mmol) in methanol (10 mL) was added oxone (0.66 g, 1.08 mmol) and water (2 mL). The reaction mixture was stirred for 24 hours at room temperature, and then the methanol was removed at reduced pressure. The
35 concentrated residue was brought up in 150 mL of ethyl acetate. The organic solution was washed with saturated aqueous NaHCO₃ (2 x 100 mL), water (2 x 100 mL), brine (2

x 100 mL), dried over MgSO_4 , filtered and concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 0.15 g (56.1 %) of the desired sulfone product as a yellow solid: HRMS: calcd for $\text{C}_{33}\text{H}_{48}\text{N}_4\text{O}_{11}\text{S}_2$ 741.2839 (M+H), found 741.2803.

EXAMPLE 57

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[[4-morpholinylcarbonyl)methyl]sulfonyl]propanamide



15 Part A: Preparation of 4-(2-chloroacetyl)morpholine

To an ice cold solution of chloroacetyl chloride (1.29 g, 11 mmol) in 10 mL of methylene chloride was added morpholine (1 g, 11 mmol) in 10 mL of methylene chloride containing triethylamine (2.32 g, 23 mmol). The reaction mixture was stirred at 5°C for 30 minutes then warmed to room temperature and stirred for 18 hours. After quenching with water (20 mL) at 5°C, additional methylene chloride (100 mL) was added. The organic layer was separated, washed with 1 N HCl (1 x 50 mL), saturated aqueous NaHCO_3 (1 x 50 mL), brine (1 x 50 mL), dried over MgSO_4 , filtered and concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 0.52 g (28.8%) of 4-(2-chloroacetyl)morpholine as a brown oil.

1H NMR (300 MHz / CDCl_3): δ 3.51-3.54 (m, 2H), 3.61-3.64 (m, 2H), 3.68-3.74 (m, 4H), 4.06 (s, 2H). HRMS: calcd for $\text{C}_6\text{H}_{10}\text{N}_1\text{O}_2\text{Cl}_1$ 164.0478, found 164.0498.

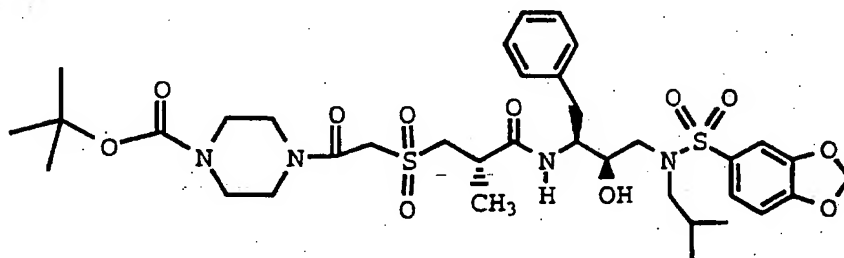
Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[[4-morpholinylcarbonyl)methyl]thio]
5 propanamide

To an ice-cold solution of N-[2R-hydroxy-3-[(2-
methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-
(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide
10 (1.60 g, 3.07 mmol) in 10 mL of dichloromethane was added
4-(2-chloroacetyl)morpholine (0.50 g, 3.07 mmol) in 5 mL
of dichloromethane containing triethylamine (0.31 g, 3.07
mmol). The ice bath was removed, and the reaction
mixture was stirred for 24 hours at room temperature.
15 The reaction mixture was then diluted with 200 mL of
dichloromethane. The organic solution was washed with 1
N HCl (2 x 100 mL), saturated aqueous NaHCO₃ (2 x 100
mL), brine (2 x 100 mL), dried over MgSO₄, filtered and
concentrated. The resulting residue was purified by
20 flash column chromatography on silica gel eluting with 80
% ethyl acetate in hexane to give 1.61 g (80.8%) of the
desired sulfide product as a pale yellow solid: HRMS
calcd for C₃₁H₄₃N₃O₈S₂ 650.2570, found 650.2583.

25 Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[[4-morpholinylcarbonyl)methyl]
sulfonyl]propanamide

30 To a solution of the sulfide compound from Part B (0.50
g, 0.77 mmol) in methanol (13 mL) was added oxone (1.66
g, 2.7 mmol) and water (1.5 mL). The reaction mixture
was stirred for 18 hours at room temperature, then cooled
in an ice-water bath, and saturated aqueous NaHCO₃ (5 mL)
35 was added. The methanol was removed at reduced pressure,
and the residue was brought up in 150 mL of methylene
chloride. The organic solution was washed with 5%

aqueous NaHCO₃ (2 x 100 mL), water (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered and the filtrate was concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 0.47 g (89.5%) of the
 5 desired sulfone as a white solid: HRMS: calcd for C₃₁H₄₃N₃O₁₀S₂ 682.2468, found 682.2454.

EXAMPLE 58

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Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[4-(t-butoxycarbonyl)piperazin-1-yl]carbonyl]methyl]sulfonylpropanamide

15

Part A: Preparation of 1-(2-chloroacetyl)-4-(tert-butoxycarbonyl)piperazine

To an ice-cold solution of chloroacetyl chloride (1.27 g, 10 mmol) in 15 mL of methylene chloride was added N-tert-butoxycarbonylpiperazine (1.27 g, 11 mmol) in 10 mL of methylene chloride containing triethylamine (2.17 g, 20 mmol). The reaction mixture was stirred at 5°C for 30 minutes, then warmed to room temperature and stirred for
 20 24 hours. Water (20 mL) was added at 5°C, and the reaction mixture was diluted with methylene chloride (200 mL). The organic layer was separated, washed with saturated aqueous NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered, and concentrated at
 25 reduced pressure. The concentrated residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give 2.20 g (84.0%) of 1-(2-

30

chloroacetyl)-4-(tert-butoxycarbonyl)piperazine as a yellow liquid. ^1H NMR (300 MHz / CDCl_3): δ 1.46 (s, 9H), 3.41-3.60 (m, 8H), 4.07 (s, 2H). HRMS: calcd for $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}_3\text{Cl}$ 262.1084, found 262.1079.

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Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[4-(t-butoxycarbonyl)piperazin-1-yl carbonyl]methyl]thio]propanamide

10

To an ice-cold solution of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.60 g, 0.96 mmol) in 10 mL of dichloromethane was added 15 1-(2-chloroacetyl)-4-(tert-butoxycarbonyl)piperazine (0.30 g, 0.96 mmol) in 5 mL of dichloromethane containing triethylamine (0.17 g, 1.43 mmol). The reaction mixture was stirred for 72 hours at room temperature. The reaction mixture was then diluted with 150 mL of 20 dichloromethane. The organic solution was washed with saturated aqueous NaHCO_3 (2 x 100 mL), brine (2 x 100 mL), dried over MgSO_4 , filtered, and the filtrate was concentrated under vacuum. The resulting residue was purified by flash column chromatography on silica gel 25 eluting with 60% ethyl acetate in hexane to give 0.57 g (79.7%) of the desired sulfide as a white solid: HRMS calcd for $\text{C}_{36}\text{H}_{52}\text{N}_4\text{O}_9\text{S}_2$ 749.3254, found 749.3266.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[4-(t-butoxycarbonyl)piperazin-1-yl carbonyl]methyl]sulfonyl]propanamide

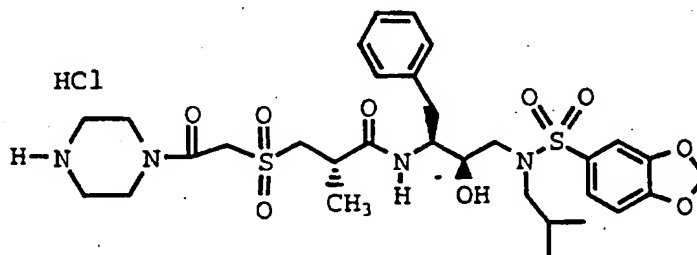
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To a solution of the sulfide product from Part B (0.30 g, 0.38 mmol) in methanol (10 mL) was added oxone (0.83 g, 1.35 mmol) and water (1.5 mL). The reaction mixture was stirred for 20 hours at room temperature. The reaction

35

mixture was cooled in an ice-water bath, and water (10 mL) was added. The methanol was then removed at reduced pressure. The concentrated residue was brought up in 150 mL of methylene chloride. The organic solution was washed with saturated aqueous NaHCO₃ (2 x 100 mL), water (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered, and the filtrate was concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 0.24 g (76.7%) of the desired sulfone product as a pale yellow solid: HRMS: calcd for C₃₆H₅₂N₄O₁₁S₂ 781.3152, found 781.3141.

EXAMPLE 59

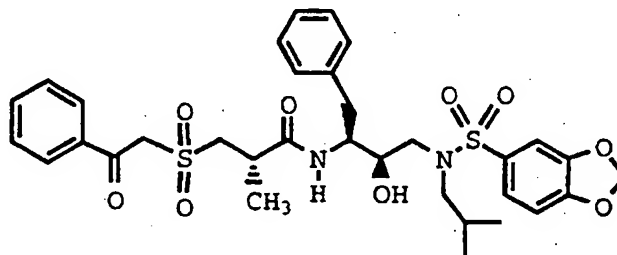


Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[4-(t-butoxycarbonyl)piperazin-1-ylcarbonyl]methyl]sulfonyl]propanamide hydrochloride

N-[2R-Hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[4-(t-butoxycarbonyl)piperazin-1-ylcarbonyl]methyl]sulfonyl]propanamide (0.15 g, 0.19 mmol) was treated with 5 mL of 4 N HCl in dioxane under nitrogen. The reaction mixture was stirred for 3 hours at room temperature, then the mixture was concentrated under reduced pressure. Toluene (several mL) was added to the concentrated residue then removed under reduced pressure. The resulting residue was dried in vacuo to give 0.12 g (87.2 %) of the desired product as a pale yellow solid: HRMS: calcd for C₃₁H₄₄N₄O₉S₂ 681.2628, found 681.2614.

EXAMPLE 60

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(phenacylsulfonyl)-propanamide



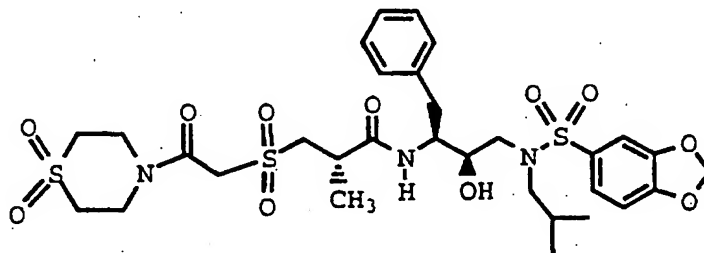
Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(phenacylthio)propanamide

To an ice-cold solution of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.1 g, 0.19 mmol) and DBU (0.032 g, 0.21 mmol) in 1 mL of anhydrous THF was added phenacyl chloride (Aldrich, 0.04 g, 0.21 mmol) dissolved in 1 mL of anhydrous THF. Then the ice bath was removed, and the reaction mixture was stirred for 20 minutes at room temperature. The THF was removed at reduced pressure, and the concentrated residue was diluted with 100 mL of ethyl acetate. The organic solution was washed with aqueous 3% KHSO₄ (2 x 50 mL), brine (2 x 50 mL), dried over MgSO₄, filtered, and the filtrate was concentrate under vacuum. The resulting residue was dried in vacuo to give 0.12 g (98.2%) of the desired sulfide product as a solid: HRMS calcd for C₃₃H₄₀N₂O₇S₂ 641.2355, found 641.2340.

Part B. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(phenacylsulfonyl)propanamide

To a solution of the sulfide product from Part A (0.05 g, 0.08 mmol) in methanol (2 mL) was added oxone (0.17 g, 0.27 mmol) and water (0.2 mL). The reaction mixture was stirred for 18 hours at room temperature. The methanol was removed at reduced pressure, and the residue was brought up in 30 mL of ethyl acetate. The organic solution was washed with 5% aqueous NaHCO₃ (1 x 20 mL), water (1 x 20 mL), brine (1 x 20 mL), dried over MgSO₄, filtered, and the filtrate was concentrated at reduced pressure. The concentrated residue was purified by flash column chromatography on silica gel eluting with 50% ethyl acetate in hexane to give 0.06 g (28.5%) of the desired sulfone as a white solid: HRMS: calcd for C₃₃H₄₀N₂O₉S₂ 673.2254, found 673.2259.

EXAMPLE 61



Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1,1-dioxothiomorpholin-1-yl)carbonyl]methylsulfonfylpropanamide

Part A: Preparation of 4-(2-chloroacetyl)thiomorpholine

To an ice-cold solution of chloroacetyl chloride (2.87 g, 25 mmol) in 15 mL of methylene chloride was added thiomorpholine (2.50 g, 24 mmol) and triethylamine (4.9 g, 48 mmol) slowly. The reaction mixture was stirred at 5°C for 30 minutes, then warmed to room temperature and

stirred for 18 hours. After quenching with water (20 mL) at 5°C, additional methylene chloride (200 mL) was added. The organic layer was separated, washed with saturated aqueous NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, filtered, and the filtrate was concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 1.83 g (42.0%) of 4-(2-chloroacetyl)thiomorpholine as a brown liquid. ¹H NMR (300 MHz / CDCl₃): δ 2.62 (t, 2H, J = 5.03 Hz), 2.68 (t, 2H, J = 4.93 Hz), 3.75 (t, 2H, J = 5.04 Hz), 3.85 (t, 2H, J = 5.04 Hz), 4.04 (s, 2H); mass spectrum, m/z = 180.2 (M+H).

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[(1,1-dioxothiomorpholin-1-yl carbonyl)methyl]thio]propanamide

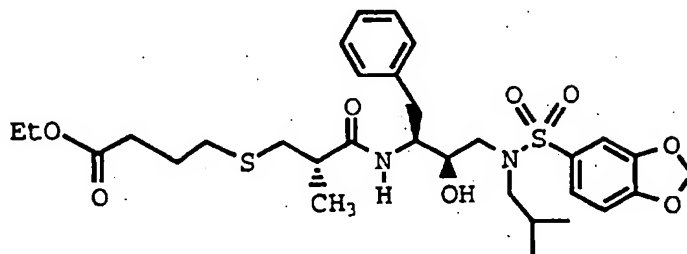
To an ice-cold solution of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.3 g, 0.57 mmol) in 5 mL of dichloromethane was added 4-(2-chloroacetyl)thiomorpholine (0.10 g, 0.57 mmol) in 5 mL of dichloromethane containing triethylamine (0.09 g, 0.86 mmol). After the addition, the ice bath was removed, and the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was then diluted with 150 mL of dichloromethane. The organic solution was washed with 1 N HCl (1 x 100 mL), saturated aqueous NaHCO₃ (1 x 100 mL), brine (2 x 100 mL), dried over MgSO₄, and filtered. The filtrate was concentrated and dried in vacuo. The resulting residue was purified by flash column chromatography on silica gel eluting with a 40-60% gradient of ethyl acetate in hexane to give 0.4 g (99%) of the desired sulfide product as a pale yellow solid: HRMS calcd for C₃₁H₄₃N₃O₇S₃ 666.2341, found 666.2370.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[(1,1-dioxothiomorpholin-1-yl
carbonyl)methyl]sulfonyl]propanamide

5

To a solution of the sulfide compound from Part B (0.28
g, 0.42 mmol) in methanol (10 mL) was added oxone (1.55
g, 2.52 mmol) and water (2 mL). The reaction mixture was
stirred for 18 hours at room temperature, and the
methanol was removed at reduced pressure. The
concentrated residue was brought up in 150 mL of ethyl
acetate. The organic solution was washed with saturated
aqueous NaHCO₃ (2 x 100 mL), water (2 x 100 mL), brine (2
x 100 mL), dried over MgSO₄, filtered, and the filtrate
was concentrated at reduced pressure. The concentrated
residue was dried in vacuo to give 0.04 g (13.0 %) of the
desired product as a white solid: HRMS: calcd for
C₃₁H₄₃N₃O₁₁S₃ 730.2138, found 730.2151.

20

EXAMPLE 62

25

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-
benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[(1,1-dioxothiomorpholin-1-yl)
carbonyl]methyl]sulfonyl]propanamide

30

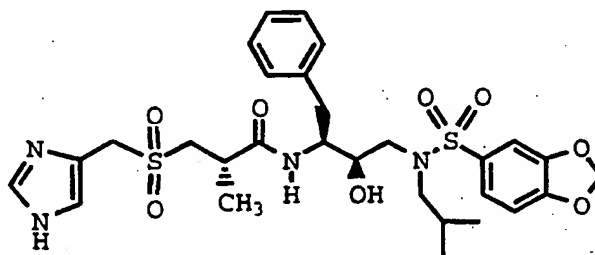
Part A: Preparation of ethyl 4-bromobutyrate

To a solution of 4-bromobutyric acid (3 g, 18 mmol) in
ethanol (30 mL) was added 5 mL of 4 N HCl in dioxane.

- The reaction mixture was stirred for 16 hours at room temperature, and then the volatile components were removed under vacuum. The concentrated residue was brought up in 150 mL of methylene chloride. The organic solution was washed with saturated aqueous NaHCO₃ (1 x 150 mL), brine (1 x 150 mL), dried over MgSO₄, filtered, and the filtrate was concentrated at reduced pressure. The concentrated residue was dried in vacuo to give 3 g (85.5%) of the known product as a yellow oil. ¹H NMR (300 MHz/CDCl₃): δ 1.22 (t, 3H, J = 7.15 Hz), 2.13 (overlapping t, 2H, J = 6.80 Hz), 2.45 (t, 2H, J = 7.15 Hz), 3.43 (t, 2H, J = 6.44 Hz), 4.10 (q, 2H, J = 7.25 Hz).
- Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[3-(ethoxycarbonyl)propylthio]propanamide
- To an ice-cold solution of ethyl 4-bromobutyrate (0.11 g, 0.574 mmol) and DBU (0.087 g, 0.574 mol) in 5 mL of THF was added N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.3 g, 0.574 mmol) in 5 mL of THF. The cold reaction mixture was warmed to room temperature and stirred 2 hours. Then the THF was removed under vacuum, and the residue was brought in 150 mL of methylene chloride. The organic solution was washed with 1 N HCl (1 x 100 mL), saturated aqueous NaHCO₃ (1 x 100 mL), brine (1 x 100 mL), dried over MgSO₄, filtered, and the filtrate was concentrated. The crude residue was purified by flash column chromatography on silica gel eluting with diethyl ether to give 0.16 g (43.8%) of the desired product as a white gummy solid:
- HRMS: calcd for C₃₁H₄₄N₂O₈S₂ 637.2617, found 637.2632.

EXAMPLE 63

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1H-imidazol-4-ylmethyl)sulfonyl] propanamide



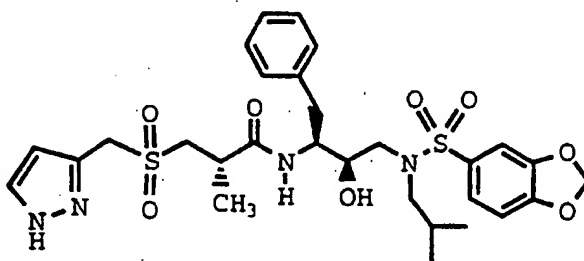
- 10 Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1H-imidazol-4-ylmethyl)thio] propanamide
- 15 To a solution of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-mercaptopropanamide (0.25 g, 0.48 mmol) in dry DMF (2.0 mL), DBU (0.163 g, 1.07 mmol) was added, and the reaction mixture was stirred under argon.
- 20 After 15 minutes, 4-chloromethylimidazole hydrochloride (0.08 g, 0.52 mmol) (prepared according to Tsung-Ying Shen, US Patent 3,438,992) was added, and the mixture was stirred at room temperature for 4 hours. The DMF was removed in vacuo, and the residue was partitioned between
- 25 ethyl acetate (25 mL) and water (10 mL). The organic layer was washed successively with saturated aqueous NaHCO₃ (2 x 10 mL), water (3 x 10 mL) and dried (Na₂SO₄). After removal of the solvent, the residue was washed with ether and filtered to give the desired sulfide as a white
- 30 powder (0.19 g), FAB-MS m/z = 603 (M+H).

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1H-imidazol-4-ylmethyl)sulfonyl] propanamide

5

The sulphide obtained in Part A, was dissolved in a mixture of methanol (4.0 mL) and water (1.0 mL), oxone (0.18 g, 0.29 mmol) was added, and the reaction mixture stirred at room temperature for 1 hour. Water (10 mL) was then added, and the reaction was cooled, neutralized with aqueous NaHCO₃ (5%) and extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed with water (3 x 15 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting substance was purified by reverse-phase HPLC using 10-90% CH₃CN-H₂O (30 minute gradient) at a 70 mL/min flow rate to give the desired imidazole sulfone as a white powder (0.078 g, 22%): R_t 14.8 min (10-90% CH₃CN-H₂O at 1 mL/min); high-resolution FAB-MS calcd for C₂₉H₃₉N₄O₈S₂ 635.2209, found 635.2196.

EXAMPLE 64



25

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1H-pyrazol-3-ylmethyl)sulfonyl] propanamide

30

Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)

propyl]-2S-methyl-3-[(1H-pyrazol-3-ylmethyl)thio]
propanamide

A mixture of 3-chloromethylpyrazole hydrochloride (0.1 g,
5 0.65 mmol) (prepared according to Tsung-Ying Shen, US
Patent 3,438,992), potassium bromide (0.1 g, 0.84 mmol)
and 18-crown-6 (0.025 g) in dry DMF (1 mL) was heated at
70°C for 2 hours under a nitrogen atmosphere. The
reaction mixture was cooled, then a solution of N-[2R-
10 hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)
sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-
mercaptopropanamide (0.25 g, 0.48 mmol) in DMF (2 mL)
containing DBU (0.2 g, 1.3 mmol) was added and stirred at
room temperature for 4 hours. The DMF was distilled away
15 in vacuo, and the residue was partitioned between ethyl
acetate (20 mL) and water (10 mL). The organic phase was
washed with brine (2 x 15 mL), dried (Na₂SO₄), and
concentrated under reduced pressure. The resulting
material was purified by flash column chromatography on
20 silica gel eluting with ethyl acetate to give the desired
pyrazole sulfide as a white amorphous substance (0.075 g,
26%). FAB-MS m/z 603 (M+H); high-resolution FAB-MS calcd
for C₂₉H₃₉N₄O₆S₂ 603.2311, found 603.2321.

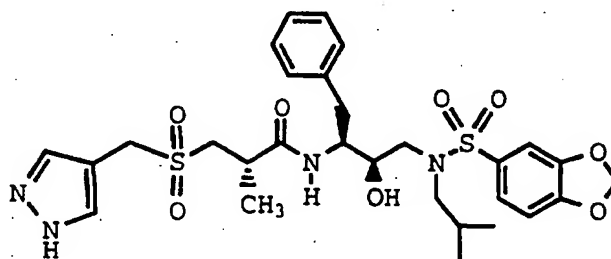
25 Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[(1H-pyrazol-3-ylmethyl)sulfonyl]
propanamide

30 The sulphide product obtained in Part A, was dissolved in
MeOH (2.0 mL) containing water (0.5 mL). Oxone (0.18 g,
0.3 mmol) was added, and the reaction mixture stirred at
0°C for 30 minutes then at room temperature for 30
minutes. The reaction mixture was concentrated under
35 reduced pressure. The resulting residue was partitioned
between saturated aqueous sodium bicarbonate (25 mL) and
EtOAc (40 mL). The organic phase was washed with brine,

dried (Na_2SO_4), and concentrated. The resulting material was purified by reverse-phase HPLC using a 5-70% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ gradient (30 min) at a 70 mL/min flow rate.

The appropriate fractions were pooled and freeze-dried to give the desired sulfone product (0.05 g, 57%) as a white powder: R_t = 16.7 min; high-resolution FAB-MS calcd for $\text{C}_{29}\text{H}_{39}\text{N}_4\text{O}_8\text{S}_2$ 635.2209, found 635.2201.

EXAMPLE 65



Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1H-pyrazol-4-ylmethyl)thio]propanamide

Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1H-pyrazol-4-ylmethyl)thio]propanamide

A mixture of 4-chloromethylpyrazole hydrochloride (0.17 g, 1.1 mmol) (prepared according to Tsung-Ying Shen, US Patent 3,438,992), KBr (0.28 g, 2.4 mmol) and 18-crown-6 (0.03 g, 0.11 mmol) in dimethylacetamide (2 mL) was stirred at ambient temperature for 4 hours, and then a solution of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercaptopropanamide (0.38 g, 0.73 mmol) in dimethylacetamide containing DBU (0.235 g, 1.5 mmol) was added. The reactants were stirred overnight at

ambient temperature, the dimethylacetamide was distilled in vacuo, and the residue was partitioned between 5% aqueous citric acid (10 mL) and ethyl acetate (25 mL). The ethyl acetate extract was washed with water (3 x 15 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The resulting substance was purified by flash column chromatography on silica gel eluting with ethyl acetate to give the desired sulfide as an amorphous white substance (0.2 g), FAB-MS m/z = 603 (M+H), high-resolution FAB-MS calcd for C₂₉H₃₉N₄O₆S₂ 603.2311, found 603.2317.

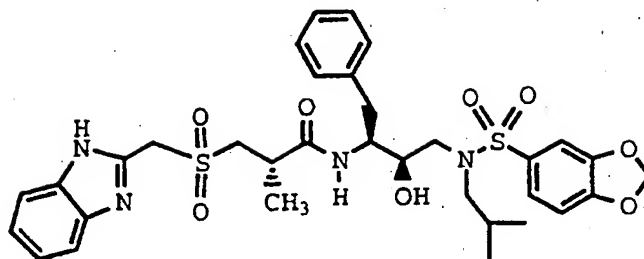
Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1H-pyrazol-4-ylmethyl)sulfonyl]propanamide

The sulfide as prepared in Part A, was dissolved in MeOH (6.0 mL), water (2.0 mL), and oxone (0.5 g, 0.8 mmol) was added. After stirring for 30 minutes at ambient temperature, the reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was partitioned between saturated aqueous sodium bicarbonate (20 mL) and ethyl acetate (40 mL). The organic phase was washed with brine, dried (Na₂SO₄) and concentrated. The resulting solid was purified by reverse-phase HPLC using a 10-90% CH₃CN/H₂O gradient (30 min) at a flow rate of 70 mL/min to give the desired sulfone as a white powder: R_t = 17.4 min; high-resolution FAB-MS calcd for C₂₉H₂₉N₄O₈S₂ 635.2209, found 635.2209.

EXAMPLE 66

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1H-benzimidazol-2-ylmethyl)sulfonyl]propanamide

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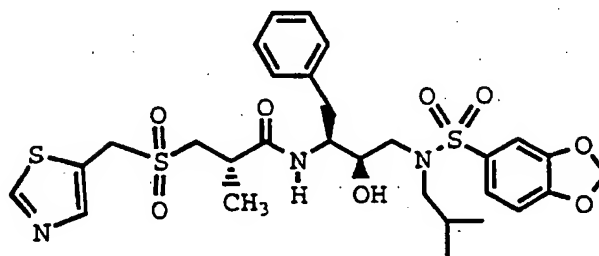
Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
 [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
 5 propyl]-2S-methyl-3-[(1H-benzimidazol-2-ylmethyl)thio]
 propanamide

A mixture of 2-(chloromethyl)benzimidazole (0.24 g, 1.44
 mmol), KBr (0.3 g, 2.5 mmol) and 18-crown-6 (0.05 g, 0.19
 10 mmol) in dimethylacetamide (2.5 mL) was stirred at room
 temperature for 2 hours, and then a solution of N-[2R-
 hydroxy-3-[(2-methylpropyl)((1,3-benzodioxol-5-yl)
 sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-
 mercaptopropanamide (0.5 g, 1 mmol) in dimethylacetamide
 15 (2.5 mL) containing DBU (0.26 g, 1.7 mmol) was added.
 After stirring the reaction mixture at room temperature
 for 2 hours, it was concentrated in vacuo, and the
 residue was partitioned between 5% aqueous citric acid
 (20 mL) and ethyl acetate (25 mL). The ethyl acetate
 20 extract was washed successively with 5% citric acid (2 x
 10 mL), water (3 x 15 mL), dried (Na₂SO₄) and
 concentrated to dryness. The residue was purified by
 flash column chromatography on silica gel eluting with
 ethyl acetate to give the desired sulfide as a pale
 25 yellow amorphous substance: R_t = 18.8 min; FAB-MS: m/z =
 653 (M+H), high-resolution FAB-MS: calcd for C₃₃H₄₁N₄O₆S₂
 653.2468, found 653.2459.

Part B. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
 30 [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
 propyl]-2S-methyl-3-[(1H-benzimidazol-2-ylmethyl)
 sulfonyl]propanamide

To a solution of the sulfide (0.22 g, 0.34 mmol) as obtained in Part A, in MeOH (6.0 mL) and water (2.00 mL), oxone (0.5 g, 0.8 mmol) was added. The reaction mixture was stirred at 10°C for 1 hour and filtered. The filtrate was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (35 mL) and saturated aqueous sodium bicarbonate (20 mL). The ethyl acetate extract was washed with water (2 x 15 mL), dried (Na₂SO₄), and concentrated to dryness. The resulting substance was purified by flash column chromatography on silica gel eluting with ethyl acetate. The appropriate fractions were combined and evaporated to give a white amorphous solid. This substance was washed with 5% ethyl acetate in ether and dried in vacuo to afford the desired sulfone as a white powder (0.15 g, 65%): *R*_T = 18.1 min; high-resolution FAB-MS calcd for C₃₃H₄₁N₄O₈S₂ 685.2366, found 685.2376.

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EXAMPLE 67

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(thiazol-5-ylmethyl)sulfonyl]propanamide

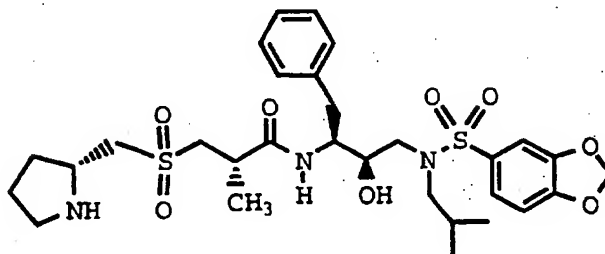
Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(thiazol-5-ylmethyl)thio]propanamide

A mixture of 5-chloromethylthiazole hydrochloride (0.22 g, 1.29 mmol) (prepared according to Bruneau, P. A. R. et. al. EP 284174; CA 110:192811), KBr (0.34 g, 2.85 mmol), 18-crown-6 (0.05 g, 0.19 mmol) in dimethyl acetamide (2.5 mL) was stirred at room temperature for 2 hours. Then a solution of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-mercaptopropanamide (0.52 g, 1 mmol) and DBU (0.36 g, 2.37 mmol) in dimethylacetamide (2.5 mL) was added. The resulting mixture was stirred at room temperature for another 2 hours and was then concentrated in vacuo. The resulting residue was partitioned between ethyl acetate (30 mL) and 5% aqueous citric acid (10 mL). The organic phase was washed with water (3 x 10 mL), dried (Na₂SO₄), concentrated to dryness and the residue was purified by flash column chromatography on silica gel eluting with 50% ethyl acetate in hexane to give the desired thiazole sulfide as a pale yellow amorphous substance (0.43 g, 72%): R_t = 18.6 min; high-resolution FAB-MS calcd for C₂₉H₃₈N₃O₆S₃ 620.1923, found 620.1913.

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(thiazol-5-ylmethyl)sulfonyl] propanamide

A mixture of the sulfide (0.15 g, 0.24 mmol) as prepared in Part A, oxone (0.33 g, 0.54 mmol) in MeOH (4.00 mL) and water (1.00 mL) was stirred at 10°C for 45 minutes and filtered. The filtrate was concentrated, and the residue was partitioned between ethyl acetate (40 mL) and aqueous saturated sodium bicarbonate (20 mL). The organic phase was washed with water, dried (Na₂SO₄) and concentrated to dryness. The resulting solid was purified by flash column chromatography on silica gel eluting with ethyl acetate. Fractions containing the

major product were combined, concentrated and dried under vacuum to give the desired sulfone product as an amorphous substance (0.12 g, 76%): R_t = 16.5 min; high-resolution FAB-MS calcd for $C_{29}H_{38}N_3O_8S_3$ 652.1821, found 652.1822.

EXAMPLE 68

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl]thio]propanamide

Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl]thio]propanamide

To a solution of L-N-Cbz-2-bromomethylpyrrolidine (0.32g, 1.07 mmol) (prepared according to J. Org. Chem. 48 (22), 4058-67, 1983) and DBU (0.2 g, 1.3 mmol) in dimethyl acetamide (3 mL), was added a solution of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-mercapto propanamide (0.5 g, 0.96 mmol) in dimethyl acetamide (2 mL), and the reaction mixture was stirred at room temperature for 2 hours under an argon atmosphere. The dimethylacetamide was distilled in vacuo, and the residue was partitioned between ethyl acetate (25 mL) and 5% aqueous citric acid (15 mL). The organic phase was

washed with water (2 x 15 mL), dried (Na₂SO₄), and concentrated. The resulting substance was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:1, v/v) to give the desired
5 pyrrolidine-substituted sulfide (0.4 g, 57%) as a white amorphous material: FAB-MS m/z 746 (M+Li); high-resolution FAB-MS calcd for C₃₈H₅₀N₃O₈S₂ 740.3039 (M+H), found 740.3022.

10 Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl]sulfonyl]propanamide

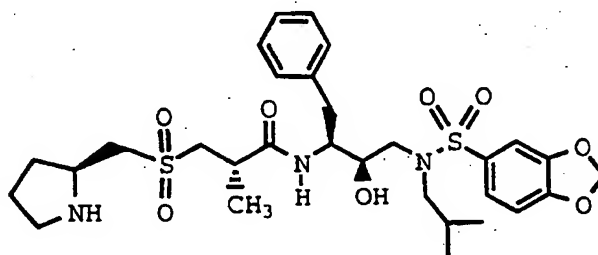
15 A mixture of the sulfide prepared as described in Part A (0.33 g, 0.45 mmol), and oxone (0.69 g, 1.1 mmol) in methanol (8.00 mL) and water (2.00 mL) was stirred at 10°C for 30 minutes. After stirring at room temperature for 1.5 hours, the mixture was filtered, and the filtrate
20 was concentrated. The resulting residue was partitioned between saturated aqueous sodium bicarbonate (15 mL) and ethyl acetate (35 mL). The organic phase was washed with water (2 x 25 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column
25 chromatography on silica gel eluting with 60% ethyl acetate in hexane to give the desired N-carbobenzyloxy-pyrrolidine-substituted sulfone (0.25 g, 74%) as an amorphous white solid: R_t = 24.7 min; high-resolution FAB-MS calcd for C₃₈H₅₀N₃O₁₀S₂ 772.2938, found 772.2931.

30 Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1H-pyrrolidin-2S-ylmethyl)sulfonyl] propanamide

35 A solution of the sulfone product from Part B (0.12 g, 0.16 mmol) in methanol (10 mL) was hydrogenated at 50 psi

in the presence of 10% Pd/C (0.15 g) at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was purified by reverse-phase HPLC using a 10-90% CH₃CN/H₂O gradient (30 min) at a flow rate of 70 mL/min to give the desired deprotected pyrrolidine-substituted sulfone (0.07 g, 60%) as a white powder: R_t = 17.2 min; high-resolution FAB-MS calcd for C₃₀H₄₄N₃O₈S₂ 638.2570, found 638.2573.

10

EXAMPLE 69

15 Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2R-ylmethyl]thio]propanamide

20 Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2R-ylmethyl]thio]propanamide

25 Following the procedure described in Example 68, Part A, N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2R-ylmethyl]thio]propanamide was prepared from (D)-N-Cbz-2-bromomethyl-pyrrolidine

30 (prepared according to Agric. Biol. Chem. 55 (1), 37-43, 1991) in 70% yield: R_t = 27.2 min; high-resolution FAB-MS calcd for C₃₈H₅₀N₃O₈S₂ 740.3039, found 740.3038.

Part B: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[[1-(benzyloxycarbonyl)pyrrolidin-2R-
5 ylmethyl]sulfonyl]propanamide

Following the procedure described in Example 68, Part B,
N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)
sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[1-
10 (benzyloxycarbonyl)pyrrolidin-2R-ylmethyl]sulfonyl]
propanamide was prepared from the (D)-N-cbz-2-pyrrolidine
sulfide of Part A above in 72% yield: $R_t = 24.9$ min;
FAB-MS $m/z = 778$ ($M + Li$); high-resolution FAB-MS calcd
for $C_{38}H_{50}N_3O_{10}S_2$ 772.2938 ($M+H$), found 772.2940.

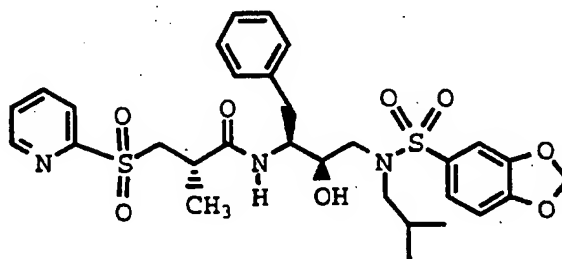
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Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[(1H-pyrrolidin-2R-ylmethyl)sulfonyl]
20 propanamide

20

Following the procedure described in Example 68, Part C,
N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)
sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-
[(1H-pyrrolidin-2R-ylmethyl)sulfonyl]propanamide was
25 prepared from the (D)-N-cbz-2-pyrrolidine sulfone of Part
B above in 85% yield: $R_t = 17.4$ min; high-resolution
FAB-MS calcd for $C_{30}H_{44}N_3O_8S_2$ ($M+H$) 638.2570, found
638.2584.

30

EXAMPLE 70

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-pyridinylsulfonyl)propanamide

5

Part A: Preparation of methyl 3-(2-pyridylthio)-2S-methylpropionate

10 To a solution of 2-mercaptopyridine (1.4 g, 12.6 mmol) in dry THF (10 mL), DBU (1.94 g, 12.75 mL) was added, and the reaction mixture was stirred at 0°C. After 15 minutes, a solution of methyl 3-bromo-2S-methylpropionate (2.0 g, 11.05 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at 0°C for 3 hours under an
15 argon atmosphere. The solution was then concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (50 mL), washed with saline (2 x 20 mL), dried (Na₂SO₄) and concentrated. The resulting material was purified by flash column chromatography on
20 silica gel eluting with 20% ethyl acetate in hexane to give methyl 3-(2-pyridylthio)-2S-methylpropionate (0.75 g, 32%) as a colorless liquid: ¹H-NMR (CD₃OD) δ: 8.41 (m, 1H), 7.6 (m, 1H), 7.23 (d, 1H, J = 8.1 Hz), 7.06 (m, 1H), 3.65 (s, 3H), 3.35 (m, 2H), 2.86 (sextet, 1H), 1.25 (d, 25 3H, J = 7.2 Hz); FAB-MS m/z 218 (M+Li), 212 (M+H); high-resolution FAB-MS calcd for C₁₀H₁₄NO₂S 212.0745 (M+H), found 212.0731.

30 Part B: Preparation of 3-(2-pyridylthio)-2S-methylpropionic acid

A mixture of methyl 3-(2-pyridylthio)-2S-methylpropionate (0.6 g, 2.8 mmol) and LiOH (0.21 g, 5 mmol) in methanol (4 mL) and water (1 mL) was stirred at room temperature
35 for 2.5 hours. After the removal of the solvents under reduced pressure, water (20 mL) was added. Then the mixture was cooled, acidified with 5% aqueous citric acid

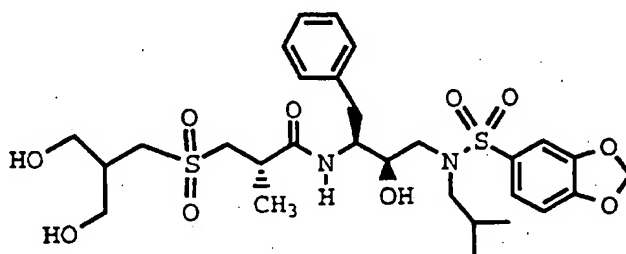
and the product was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with saline (2 x 20 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford the acid (0.48 g, 86%) as a pale yellow powder: ¹H-NMR (CD₃OD) δ: 8.36 (m, 1H), 7.58 (m, 1H), 7.26 (d, 1H, J = 8.1 Hz), 7.06 (m, 1H), 3.36 (m, 2H), 2.78 (sextet, 1H), 1.26 (d, 3H, J = 7.2 Hz); FAB-MS m/z 198 (M+H); high-resolution FAB-MS calcd for C₉H₁₂O₂NS 198.0589, found 198.0573.

Part C: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-pyridinylthio)propanamide

To a solution of 3-(2-pyridylthio)-2S-methylpropionic acid (0.5 g, 2.54 mmol) and HOBt (0.6 g, 4 mmol) in dimethylformamide (5 mL) was added EDC (0.5 g, 3.1 mmol) and the reaction mixture was stirred at 0°C for 1 hour. Then a solution of 1-[N-[(1,3-benzodioxol-5-yl)sulfonyl]-N-(2-methylpropyl)amino]-3(S)-amino-4-phenyl-2(R)-butanol (0.97 g, 2.3 mmol) in CH₂Cl₂ (5 mL) was added, and the mixture was stirred at room temperature for 4 hours. The solvents were distilled in vacuo, and the residue was partitioned between saturated aqueous sodium bicarbonate (25 mL) and ethyl acetate (45 mL). The organic phase was washed successively with saturated aqueous sodium bicarbonate (2 x 20 mL), water, dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:1, v/v) to give the desired sulfide (1.2 g, 87%) as an amorphous 1:4 diastomeric mixture: high-resolution FAB-MS calcd for C₃₀H₃₈N₃O₆S₂ 600.2202, found 600.2200.

Part D: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-(2-pyridinylsulfonyl)propanamide

To a solution of the sulfide (0.5 g, 0.83 mmol) of Part C in methanol (8 mL) and water (2.0 mL), oxone (1.3 g, 2.1 mmol) was added, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was filtered, and the filtrate was treated with cold saturated aqueous sodium bicarbonate (50 mL), then extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with water (2 x 20 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with 80% ethyl acetate in hexane to give the desired sulfone (0.38 g, 72%) as a white amorphous product: R_t = 20.4 min; high-resolution FAB-MS calcd for C₃₀H₃₈N₃O₈S₂ 632.2100, found 632.2127.

EXAMPLE 71

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-benzodioxol-5-yl)sulfonyl]aminol-1S-(phenylmethyl)propyl]-2S-methyl-3-[[[(1,3-dihydroxyprop-2-yl)methyl]sulfonyl]propanamide

Part A. Preparation of 1,3-O-benzylidene-2-(hydroxymethyl)propane

To a solution of 2-(hydroxymethyl)-1,3-propanediol (0.5 g, 4.7 mmol) and benzaldehyde (1.04 g, 9.8 mmol) in CH₂Cl₂ (5.00 mL), p-toluenesulfonic acid (0.1 g) was added, and the reaction mixture was stirred at room

temperature for 3 hours. The reaction mixture was filtered, and CH_2Cl_2 (20 mL) was added to the filtrate. The filtrate was washed with saturated aqueous sodium bicarbonate (2 x 20 mL), water (2 x 20 mL), dried (Na₂SO₄) and concentrated to dryness. The resulting residue was purified by flash column chromatography on silica gel eluting with 30% ethyl acetate in hexane to give the desired 1,3-O-benzylidene-2-(hydroxymethyl)propane as a white solid: ¹H-NMR (CD₃OD) δ : 7.5-7.3 (m, 5H), 5.54 & 5.46 (s, 1H), 4.3-4.1 (m, 3H), 3.94 (d, 1H, J = 7.8 Hz), 3.75 (t, 1H), 3.43 (d, 1H, J = 6.0 Hz), 2.3 & 1.6 (m, 1H); FAB-MS m/z = 201 (M+Li); high-resolution FAB-MS calcd for C₁₁H₁₅O₃ 195.1021 (M+H), found 195.1027.

15

Part B. Preparation of 1,3-O-benzylidene-2-(iodomethyl)propane

To a cold solution (0°C) of 1,3-O-benzylidene-2-(hydroxymethyl)propane (0.45 g, 2.32 mmol) in acetonitrile (4 mL), a solution of methyltriphenoxyphosphonium iodide (1.2 g, 2.65 mmol) was added, and the reaction mixture was stirred at 0°C. After 30 minutes, the reaction mixture was stirred at room temperature for 3 hours and then concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with cold 0.25 N NaOH (2 x 20 mL), water (3 x 20 mL), dried (Na₂SO₄) and concentrated to dryness. The resulting material was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:1, v/v) to give the desired iodo derivative as a pale yellow liquid: ¹H-NMR (CD₃OD) δ : 7.43-7.3 (m, 5H), 5.52 & 5.43 (s, 1H), 4.35-4.2 (m, 3H), 3.65 (m, 2H), 3.01 (d, 1H, J = 6.9 Hz), 2.2 & 1.85 (m, 1H); FAB-MS m/z = 305 (M+H); high-resolution FAB-MS calcd for C₁₁H₁₄IO₂ 305.0038 (M+H), found 305.0043.

Part C. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[(1,3-O-benzylideneprop-2-yl) methyl]thio]propanamide

5

To a solution of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-mercaptopropanamide (0.64 g, 1.2 mmol), in dimethylacetamide (5.0 mL), DBU (0.2 g, 1.3 mmol) was added, followed by the addition of the iodo derivative (0.45 g, 1.48 mmol) from Part B. The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo. The resulting residue was partitioned between ethyl acetate (40 mL) and 5% aqueous citric acid (20 mL). The organic phase was separated, washed with water (2 x 20 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:1, v/v) to furnish the desired sulfide (0.53 g, 62%) as a white amorphous solid: high-resolution FAB-MS calcd for C₃₆H₄₇N₂O₈S₂ 699.2744, found 699.2800.

25

Part D. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[(1,3-O-benzylideneprop-2-yl)methyl] sulfonyl]propanamide

30

A mixture of the sulfide (0.5 g, 0.72 mmol) from Part C and oxone (1.1 g, 1.78 mmol) in methanol (8.00 mL) and water (2.00 mL) was stirred at 10°C for 1 hour, and filtered. The filtrate was concentrated, 10% aqueous sodium bicarbonate (25 mL) was added, and the mixture was extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine, dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with

35

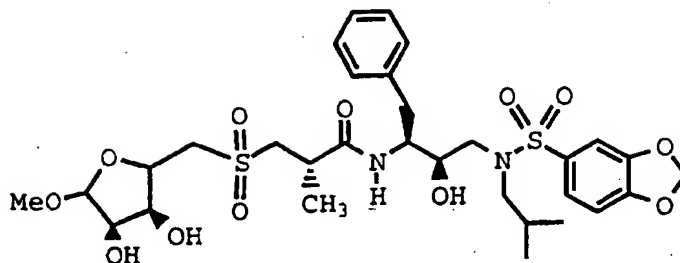
ethyl acetate to give the desired sulfone (0.25 g, 48%) as a white powder: R_t = 20.7 min; high-resolution FAB-MS calcd for $C_{36}H_{47}N_2O_{10}S_2$ 731.2672, found 731.2687.

- 5 Part E. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[[[(1,3-dihydroxyprop-2-yl)methyl] sulfonyl]propanamide
- 10 A solution of the sulfone (0.2 g, 0.27 mmol) from Part D in ethanol (5.0 mL) containing p-toluensulfonic acid (0.06 g, 0.3 mmol) was heated to reflux under a nitrogen atmosphere. After 1.5 hours, the solution was
- 15 concentrated, and the residue was partitioned between ethyl acetate (25 mL) and saturated aqueous sodium bicarbonate (10 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated to dryness. The
- 20 resulting material was purified by reverse-phase HPLC using 10-90% CH_3CN/H_2O (30 min gradient) as the mobile phase flowing at a rate of 70 mL/min. The appropriate
- fractions were combined and freeze-dried to give a white powder. This material was dissolved in 0.25 N NaOH (2 mL) and methanol (3 mL), then stirred at room temperature for
- 25 45 minutes and concentrated. The residue was partitioned between ethyl acetate (15 mL) and water (15 mL). The organic phase was washed with brine, dried (Na_2SO_4),
- concentrated and the residue was dried in vacuo to afford the desired product (0.06 g, 34%) as a white powder: R_t =
- 30 17.85 min; high-resolution FAB-MS calcd for $C_{29}H_{43}N_2O_{10}S_2$ 643.2359, found 643.2386.

EXAMPLE 72

- Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-
- 35 benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[(1-methyl-5-deoxy-D-ribofuranosyl-5-
yl)sulfonyl]propanamide

161



Part A: Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
 [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
 5 propyl]-2S-methyl-3-[(1-methyl-2,3-O-isopropylidene-5-
 deoxy-D-ribofuranosyl-5-yl)thio]propanamide

To a solution of N-[2R-hydroxy-3-[(2-methylpropyl)][(1,3-
 benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-
 10 2S-methyl-3-mercaptopropanamide (1.00 g, 1.9 mmol) in
 dimethylacetamide, (3.00 mL), DBU (0.35 g, 2.3 mmol) and
 methyl-2,3-O-iso-propylidene-5-O-(p-tolyl sulfonyl)-D-
 riboside (0.75 g, 2.1 mmol) were added, and the reaction
 mixture was stirred at room temperature for 2 hours. The
 15 DMA was distilled in vacuo, and the residue was
 partitioned between 5% aqueous citric acid (30 mL) and
 ethyl acetate (60 mL). The organic phase was washed with
 water (2 x 25 mL), dried (Na₂SO₄), and concentrated. The
 resulting residue was purified by flash chromatography on
 20 silica gel eluting with 35% ethyl acetate in hexane (v/v)
 to give the desired sulfide (0.9g, 66%) as a white
 amorphous solid: R_t = 24.4 min; high-resolution FAB-MS
 calcd for C₃₄H₄₉N₂O₁₀S₂ 709.2829, found 709.2813.

25 Part B. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
 [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
 propyl]-2S-methyl-3-[(1-methyl-2,3-O-isopropylidene-5-
 deoxy-D-ribofuranosyl-5-yl)sulfonyl]propanamide

30 A mixture of the sulfide (0.45 g, 0.64 mmol) from Part A,
 and oxone (0.9 g, 1.46 mmol), in methanol (8.00 mL) and
 water (2.00 mL) was stirred at 10°C for 1.5 hours, and

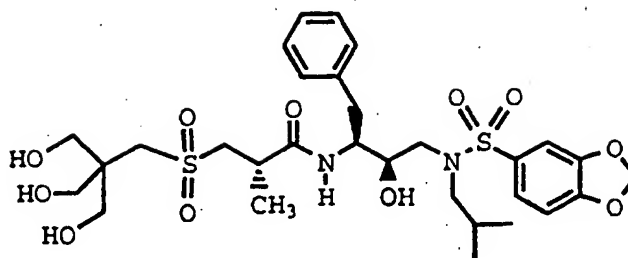
filtered. The filtrate was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (25 mL) and saturated aqueous sodium bicarbonate (25 mL). The organic phase was separated, washed with
5 water (2 x 25 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash chromatography on silica gel eluting with ethyl acetate in hexane (1:1, v/v) to give the desired sulfone (0.3 g, 64%) as a white amorphous powder: R_t = 23.3 min; high-resolution FAB-MS
10 calcd for C₃₄H₄₉N₂O₁₂S₂ 741.2727, found 741.2723.

Part C. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1-methyl-5-deoxy-D-ribofuranosyl-5-yl)sulfonyl]propanamide
15

To a solution of the sulfone (0.2 g, 0.27 mmol) from Part B in methanol (4.00 mL) and water (1.00 mL), p-toluenesulfonic (0.025 g, 0.13 mmol) was added, and the
20 reaction mixture was heated to reflux under a nitrogen atmosphere for 4 hours. The solution was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate (10 mL). The organic phase was
25 separated, washed with water (2 x 10 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give the desired product (0.12 g, 63%) as an amorphous powder: R_t = 16.6 min; high-resolution
30 FAB-MS calcd for C₃₁H₄₅N₂O₁₂S₂ 701.2414, found 701.2410.

EXAMPLE 73

Preparation of N-[2R-hydroxy-3-[(2-methylpropyl) [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl) propyl]-2S-methyl-3-[(1-methyl-5-deoxy-D-ribofuranosyl-5-yl)sulfonyl]propanamide
35



Part A. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
5 [(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-[[2-hydroxymethyl-1,3-dihydroxyprop-
2-yl)methyl]thio]propanamide

To a solution of N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-
10 benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
propyl]-2S-methyl-3-mercaptopropanamide (0.4 g, 0.77
mmol) in dimethylacetamide (3.00 mL), DBU (0.204 g, 1.3
mmol) and 2-(bromomethyl)-2-(hydroxymethyl)-1,3-
propanediol (0.19 g, 0.95 mmol) were added. The
15 resulting reaction mixture was stirred at room
temperature for 1.5 hours and at 70°C for 30 minutes.
The DMA was distilled away in vacuo, and the residue was
partitioned between 5% aqueous citric acid (10 mL) and
ethyl acetate (25 mL). The organic phase was washed with
20 water (2 x 25 mL), dried (Na₂SO₄), and concentrated. The
resulting residue was purified by flash column
chromatography on silica gel eluting with 4% methanol in
ethyl acetate to give the desired sulfide (0.22 g, 45%)
as a white amorphous solid: FAB-MS m/z = 641 (M+H),
25 high-resolution FAB-MS m/z calcd for C₃₀H₄₅N₂O₉S₂
641.2567 (M+H), found 641.2568.

Part B. Preparation of N-[2R-hydroxy-3-[(2-methylpropyl)
[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)
30 propyl]-2S-methyl-3-[[2-hydroxymethyl-1,3-dihydroxyprop-
2-yl)methyl]sulfonyl]propanamide

A mixture of the sulfide (0.20 g, 0.31 mmol) from Part A, and oxone (0.45 g, 0.73 mmol), in methanol (4.00 mL) and water (1.00 mL) was stirred at 10°C for 1.5 hours and then filtered. The filtrate was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate (20 mL). The organic phase was washed with water (2 x 25 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography on silica gel eluting with 4% methanol in ethyl acetate to give the desired sulfone product (0.12 g, 57%) as a white amorphous powder: R_t = 18.4 min; FAB-MS m/z = 673 (M+H), high-resolution FAB-MS m/z calcd for C₃₀H₄₅N₂O₁₁S₂ 673.2465 (M+H), found 673.2481.

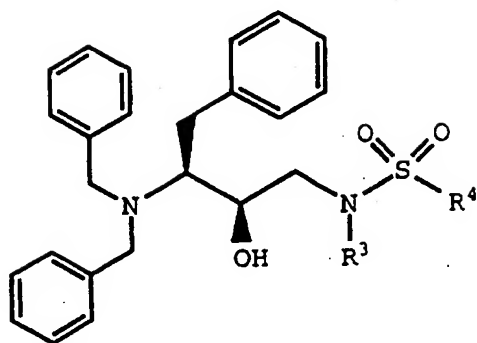
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EXAMPLE 74

Following the procedures of the previous Examples, the compounds set forth in Tables 2 through 13 can be prepared.

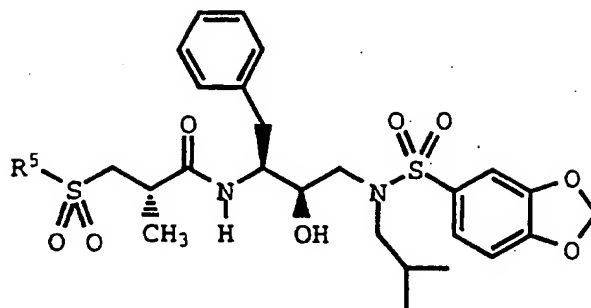
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TABLE 2



| 5 | Entry | | |
|----|-------|-------------------|-----------------------------------|
| | | R ³ | R ⁴ |
| | 1 | isobutyl | 2-methyl-1,3-benzodioxol-5-yl |
| | 2 | isobutyl | 2-methyl-1,3-benzodioxol-5-yl |
| | 3 | cyclopentylmethyl | 2-methyl-1,3-benzodioxol-5-yl |
| | 4 | cyclohexylmethyl | 2-methyl-1,3-benzodioxol-5-yl |
| 10 | 5 | cyclopentylmethyl | 1,3-benzodioxol-5-yl |
| | 6 | cyclohexylmethyl | 1,3-benzodioxol-5-yl |
| | 7 | cyclopentylmethyl | benzofuran-5-yl |
| | 8 | cyclohexylmethyl | benzofuran-5-yl |
| | 9 | cyclopentylmethyl | 2,3-dihydrobenzofuran-5-yl |
| 15 | 10 | cyclohexylmethyl | 2,3-dihydrobenzofuran-5-yl |
| | 11 | isobutyl | 1,3-benzodioxol-5-yl |
| | 12 | isobutyl | benzofuran-5-yl |
| | 13 | isobutyl | 2,3-dihydrobenzofuran-5-yl |
| | 14 | isobutyl | 1,4-benzodioxan-6-yl |
| 20 | 15 | isoamyl | 1,3-benzodioxol-5-yl |
| | 16 | isoamyl | 2,3-dihydrobenzofuran-5-yl |
| | 17 | isoamyl | 1,4-benzodioxan-6-yl |
| | 18 | isobutyl | benzothiazol-6-yl |
| | 19 | isobutyl | 2-amino-benzothiazol-6-yl |
| 25 | 20 | isobutyl | benzoxazol-5-yl |
| | 21 | cyclopentylmethyl | 2,2-difluoro-1,3-benzodioxol-5-yl |
| | 22 | cyclohexylmethyl | 2,2-difluoro-1,3-benzodioxol-5-yl |

TABLE 3A



5

Entry

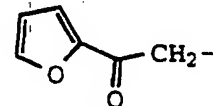
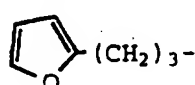
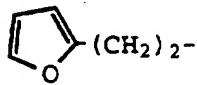
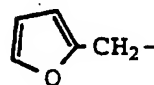
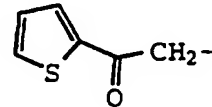
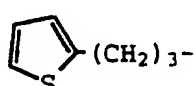
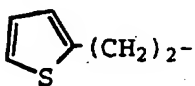
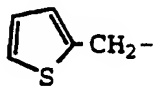
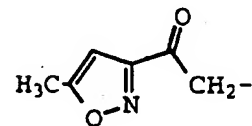
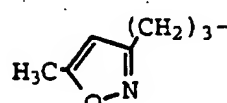
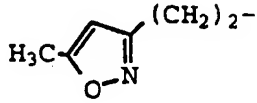
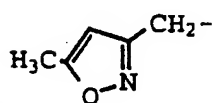
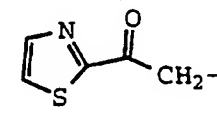
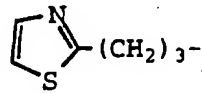
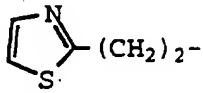
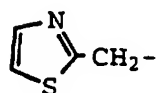
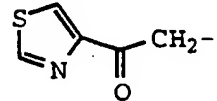
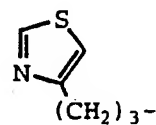
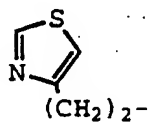
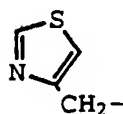
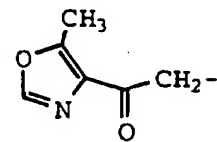
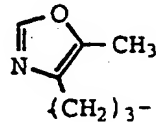
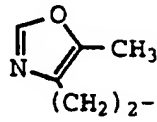
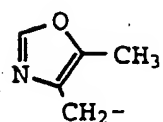
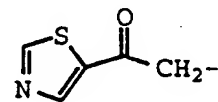
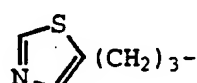
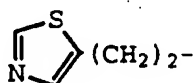
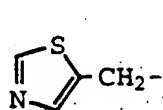
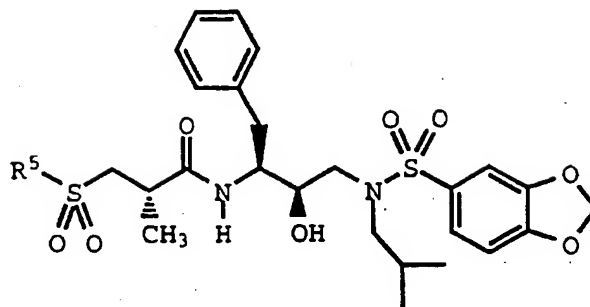
R⁵

TABLE 3B



5

Entry

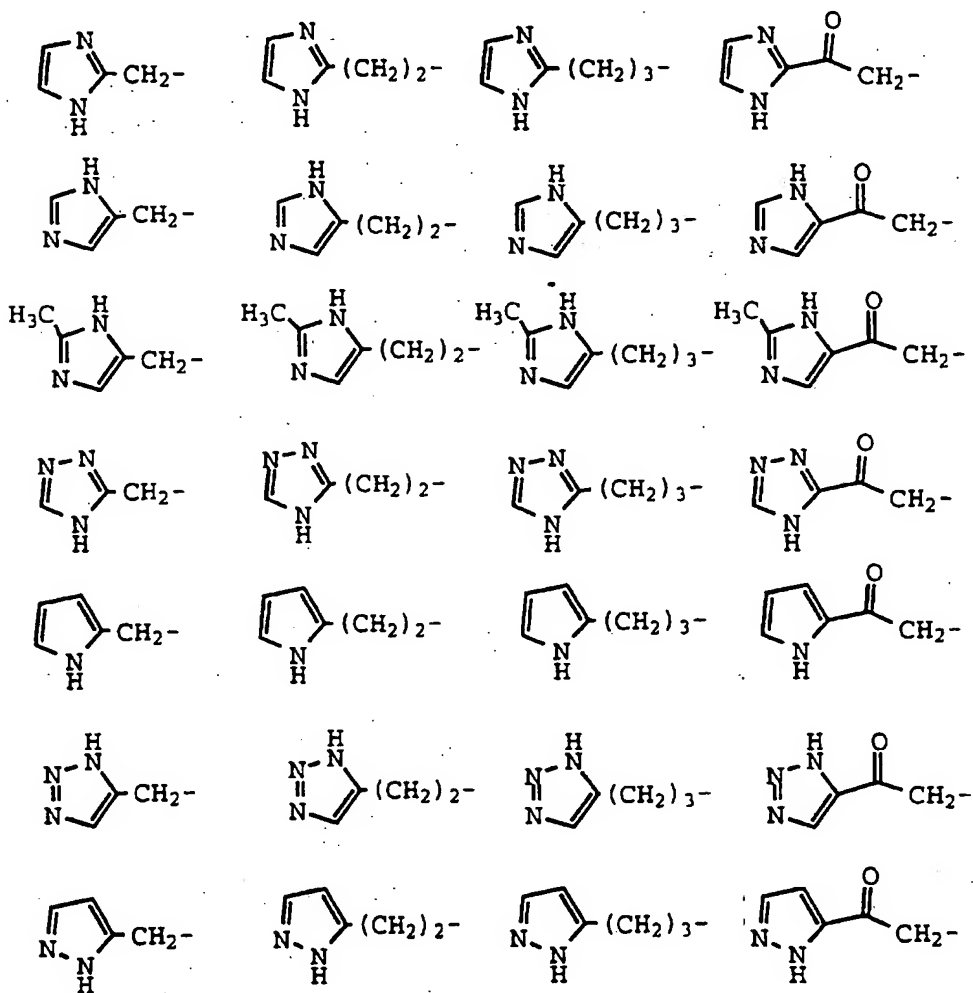
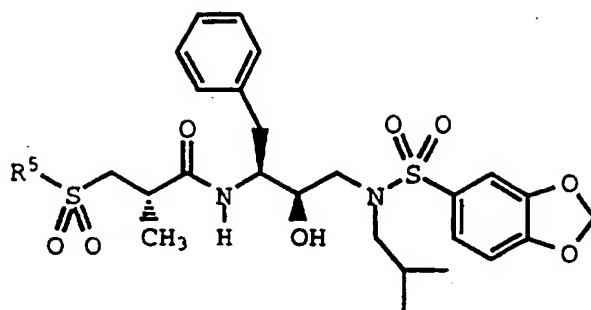
R⁵

TABLE 3C



5

Entry

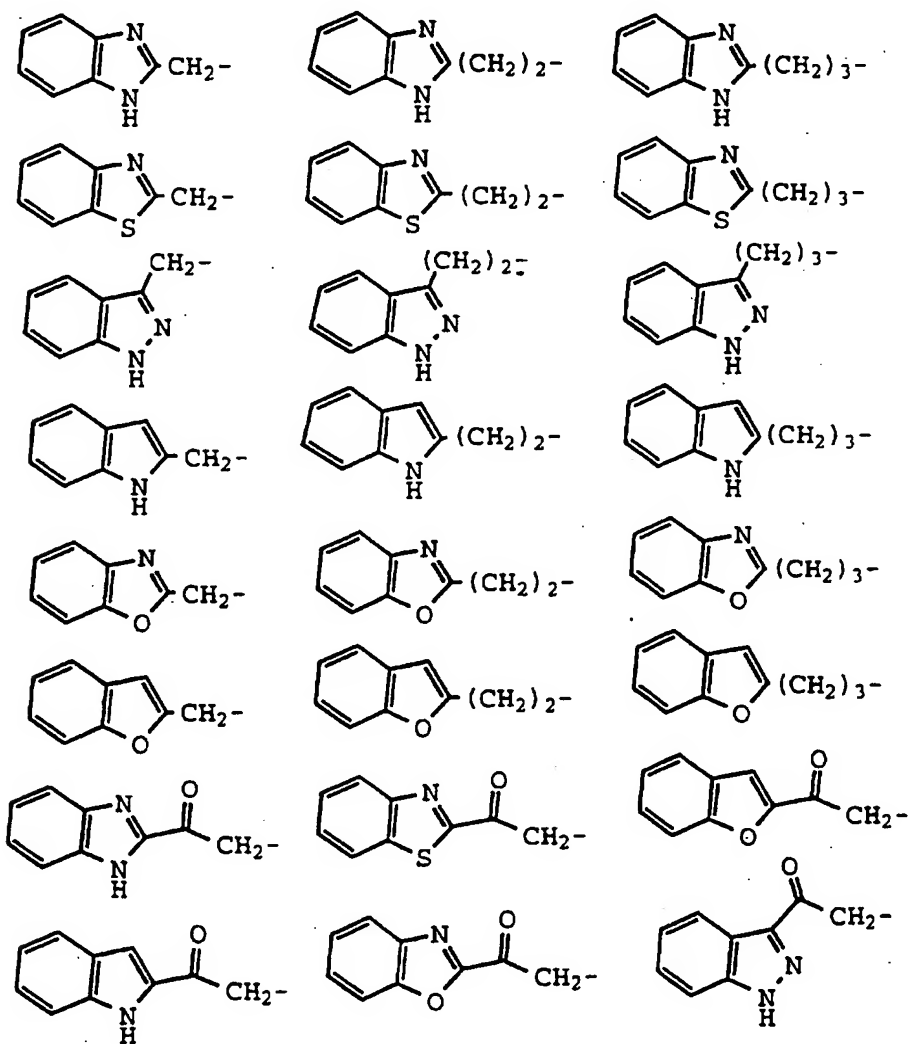
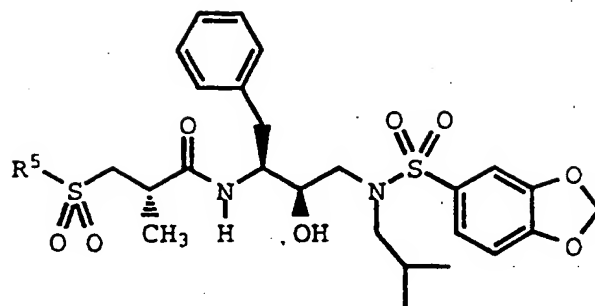
R⁵

TABLE 3D



| 5 | Entry | R ⁵ |
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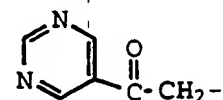
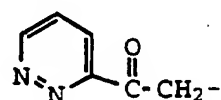
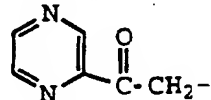
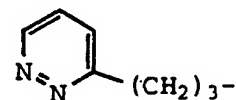
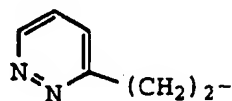
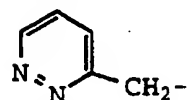
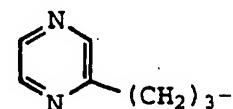
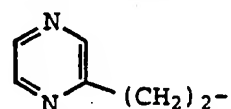
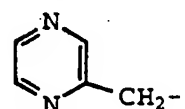
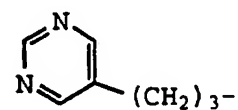
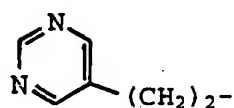
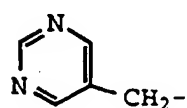
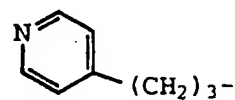
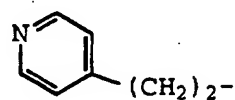
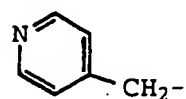
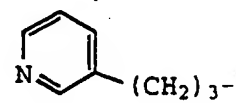
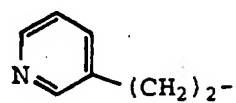
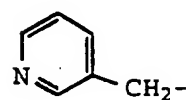
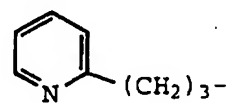
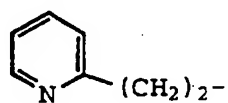
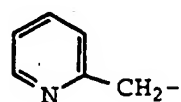
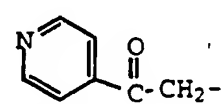
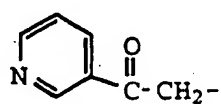
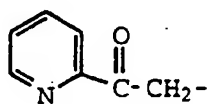
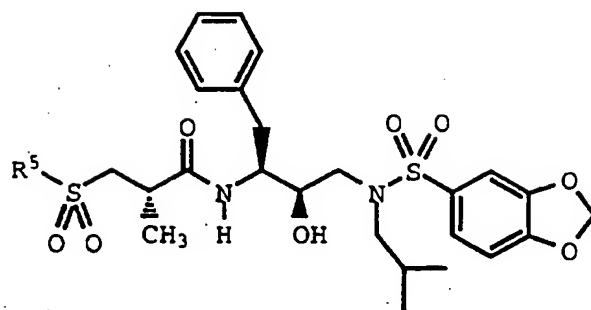
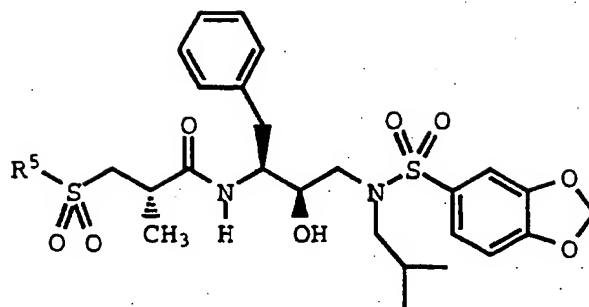


TABLE 3E



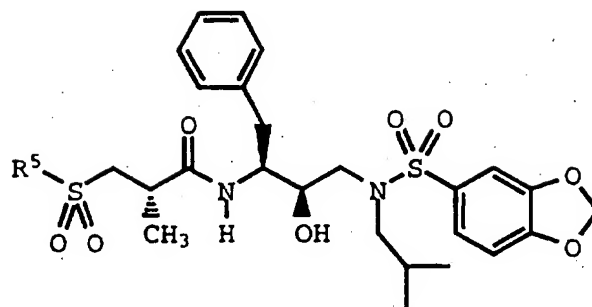
| 5 | Entry | R ⁵ |
|---|-------|----------------|
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TABLE 3F



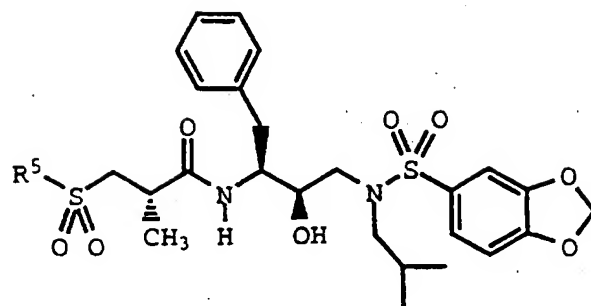
| 5 | Entry | R ⁵ | | |
|---|-------|----------------|--|--|
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TABLE 3G



| 5 | Entry | R ⁵ |
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TABLE 3H



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Entry

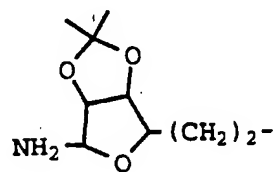
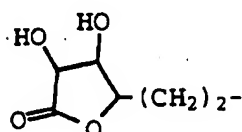
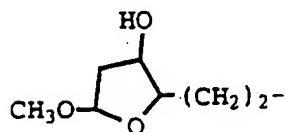
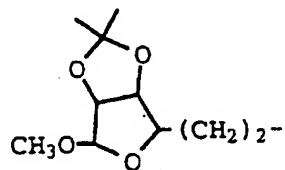
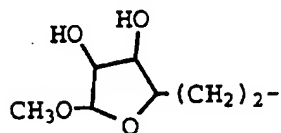
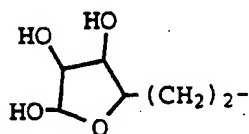
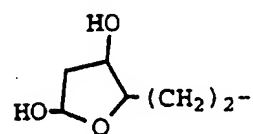
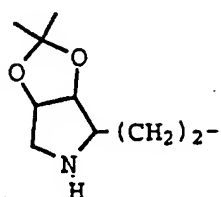
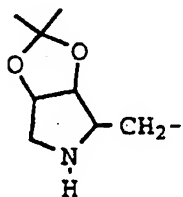
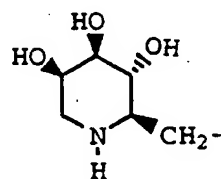
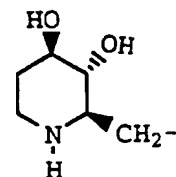
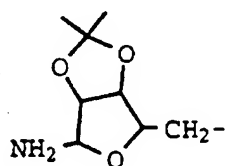
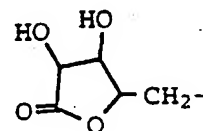
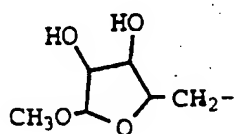
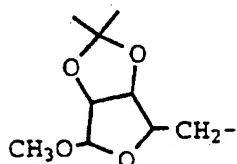
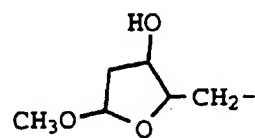
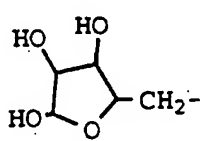
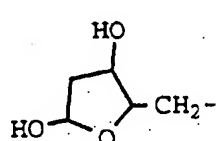
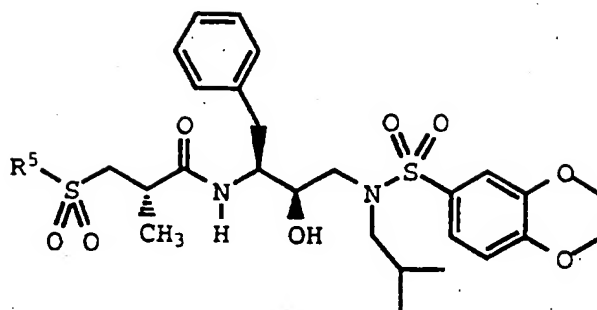
R⁵

TABLE 4A



5

Entry

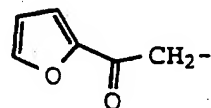
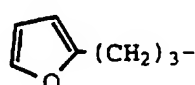
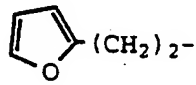
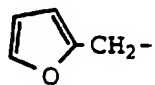
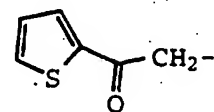
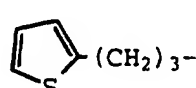
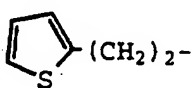
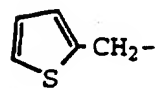
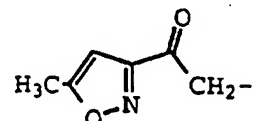
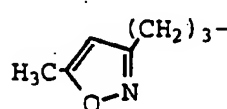
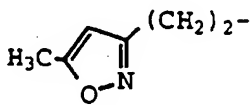
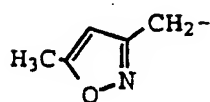
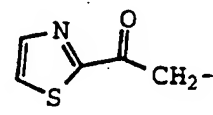
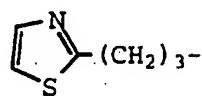
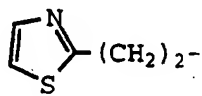
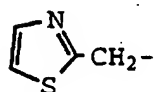
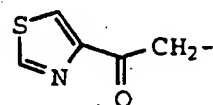
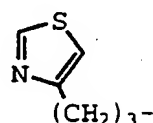
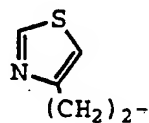
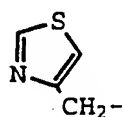
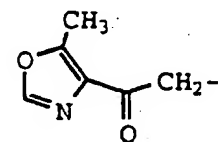
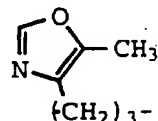
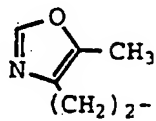
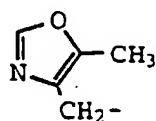
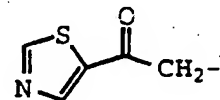
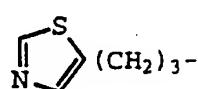
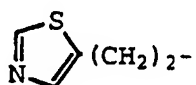
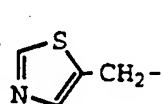
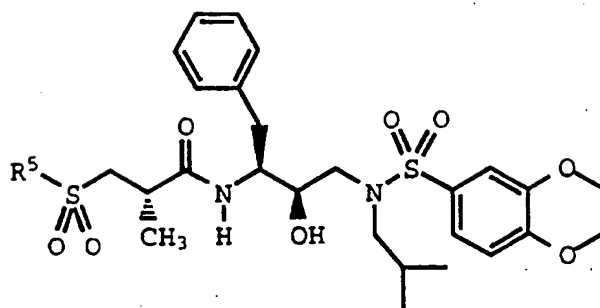
R⁵

TABLE 4B



5

Entry

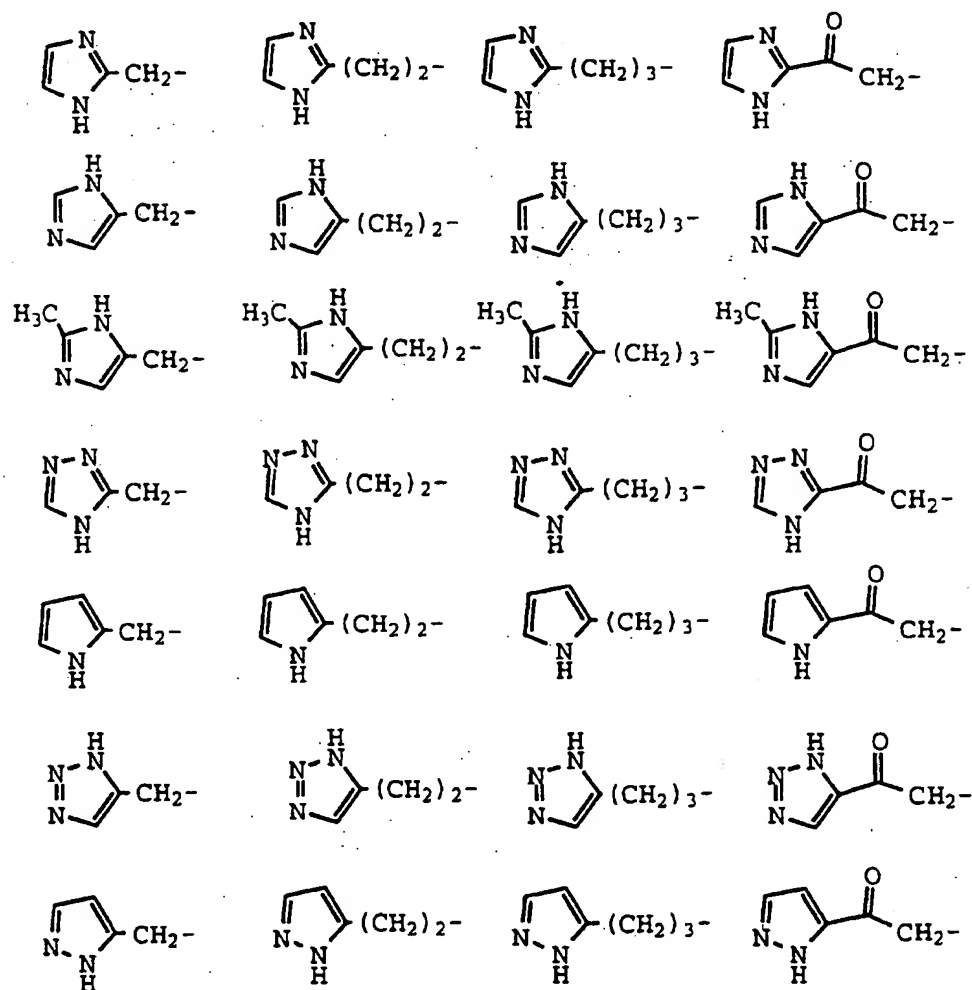
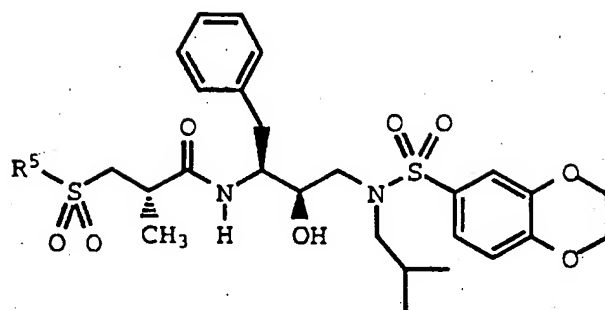
 R^5 

TABLE 4C



5

Entry

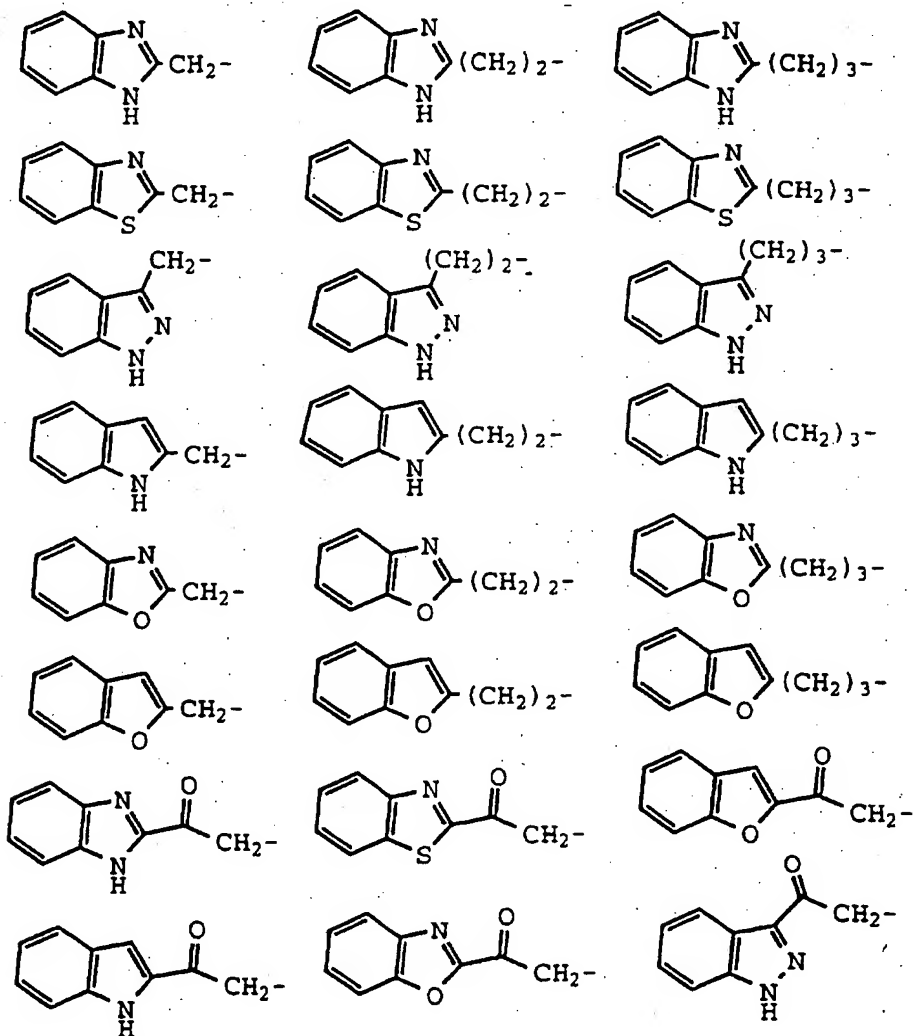
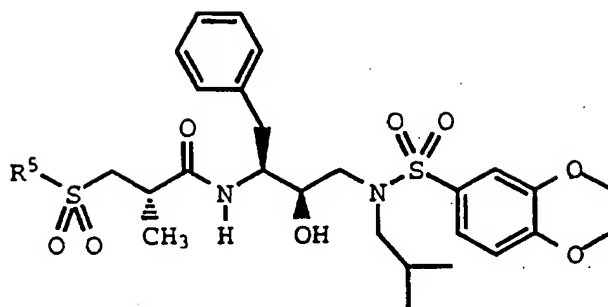
R⁵

TABLE 4D



5

Entry

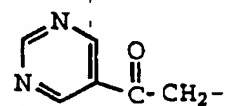
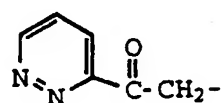
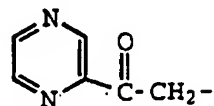
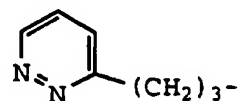
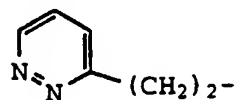
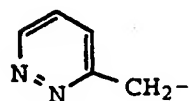
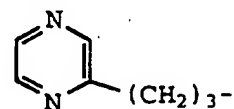
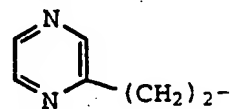
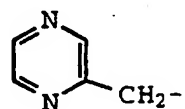
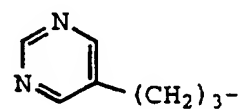
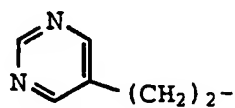
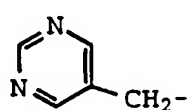
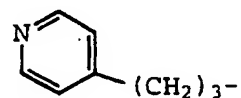
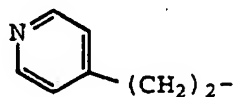
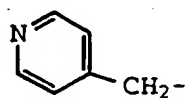
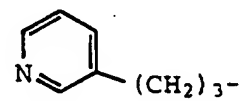
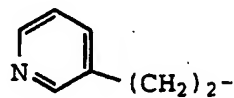
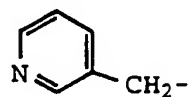
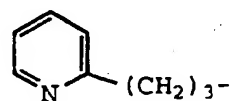
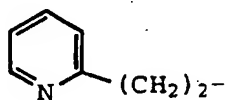
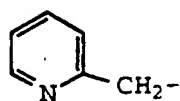
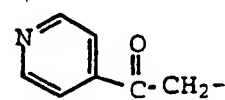
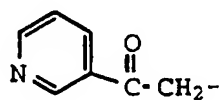
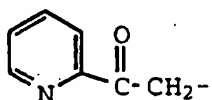
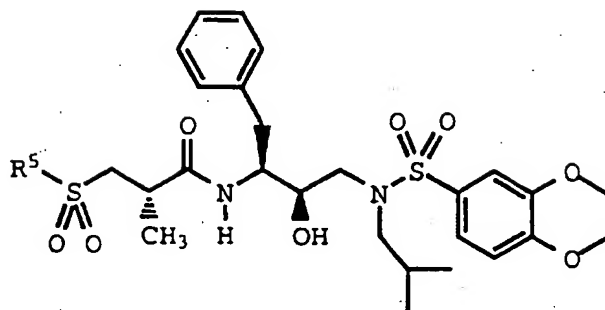
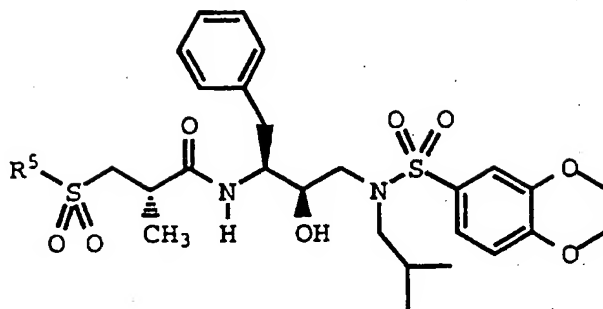
R⁵

TABLE 4E



| 5 | Entry | R ⁵ |
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TABLE 4F



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Entry

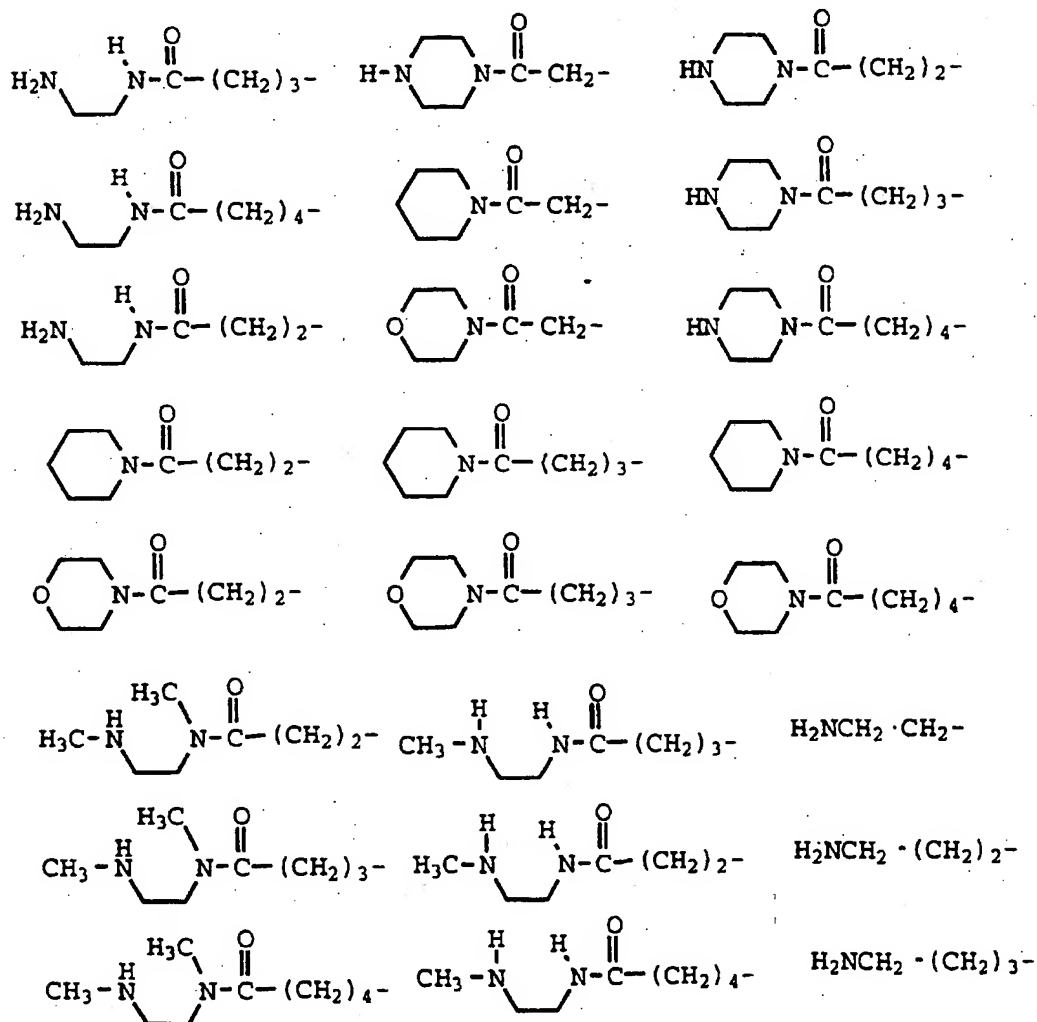
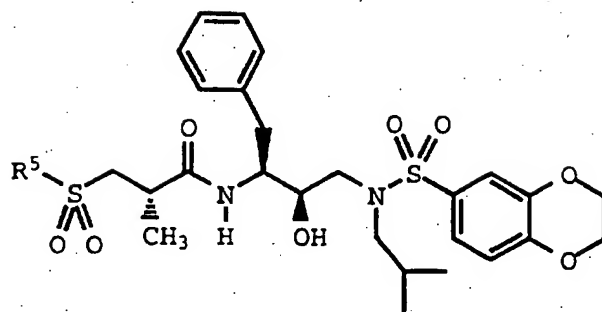
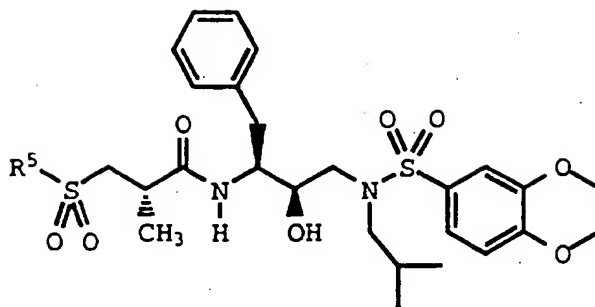
R⁵

TABLE 4G



| 5 | Entry | R ⁵ |
|---|-------|----------------|
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TABLE 4H



5

Entry

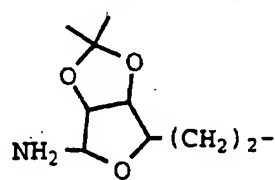
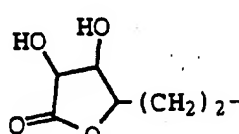
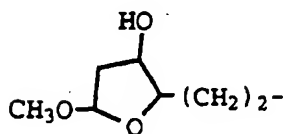
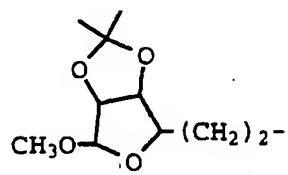
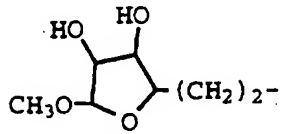
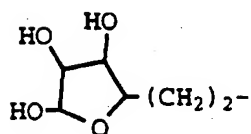
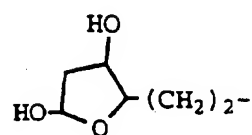
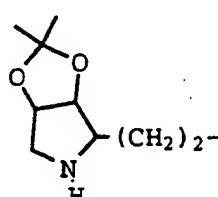
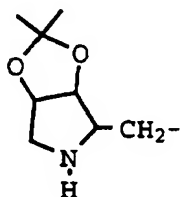
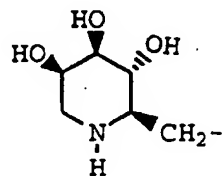
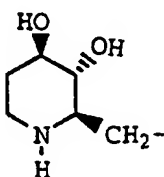
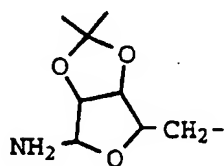
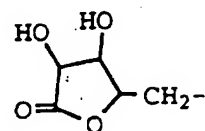
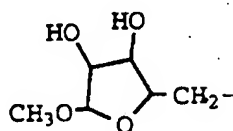
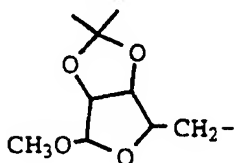
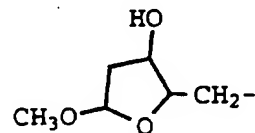
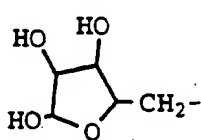
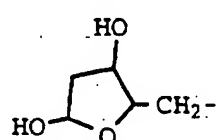
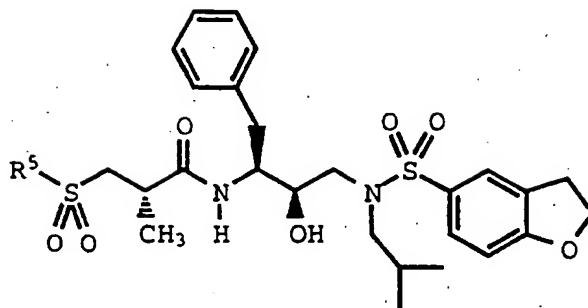
R⁵

TABLE 5A



5

Entry

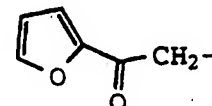
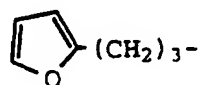
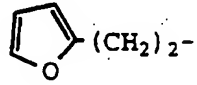
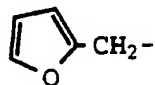
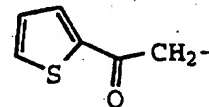
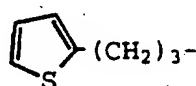
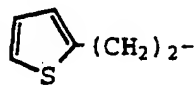
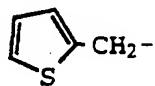
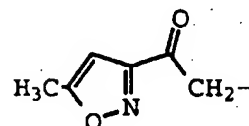
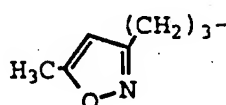
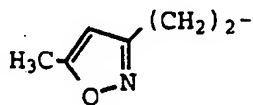
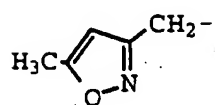
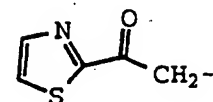
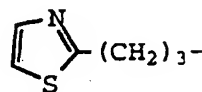
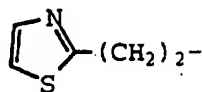
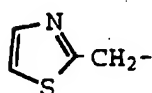
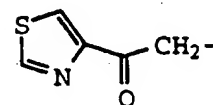
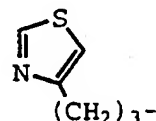
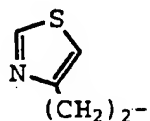
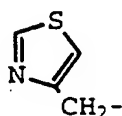
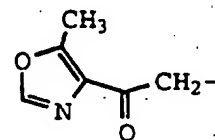
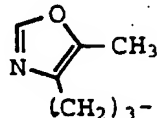
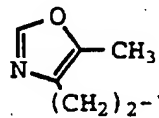
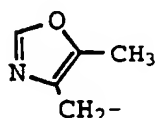
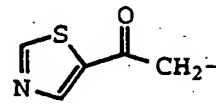
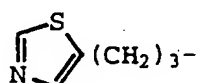
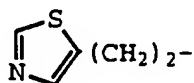
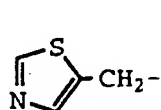
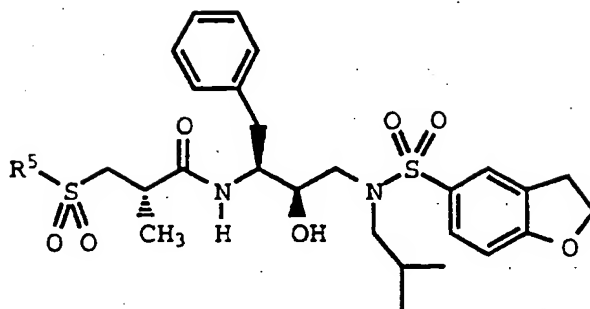
R⁵

TABLE 5B



5.

Entry

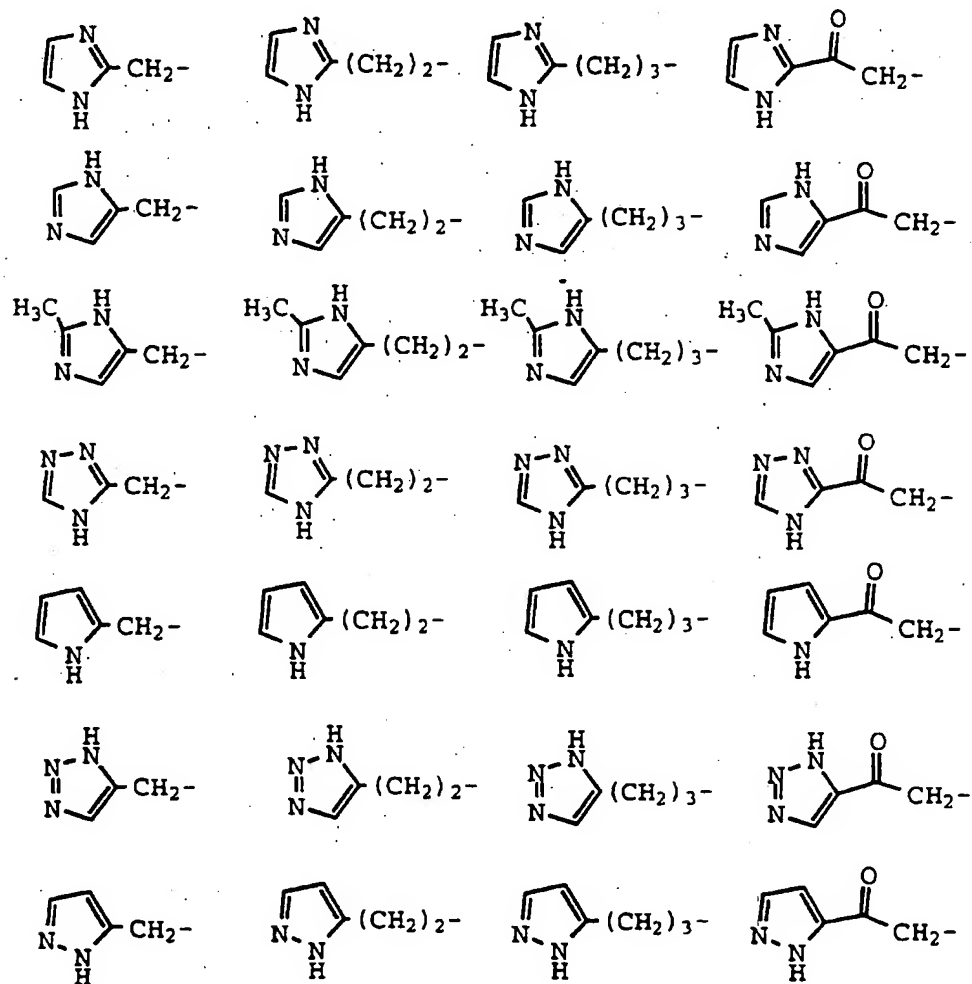
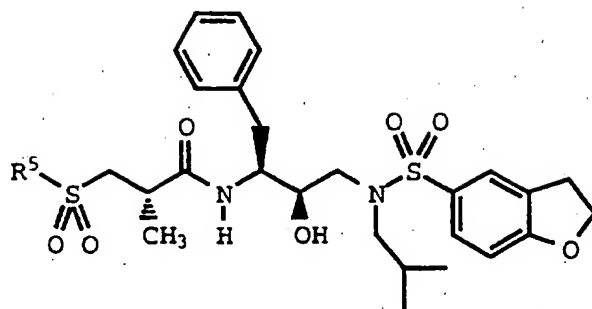
R⁵

TABLE 5C

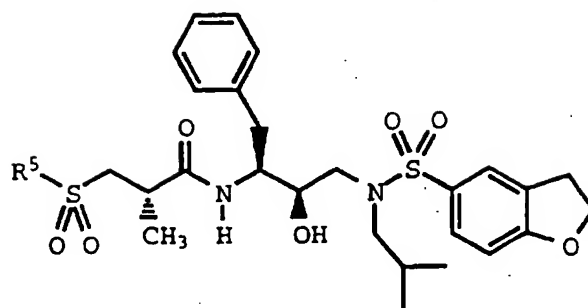


5

Entry

R⁵

TABLE 5D



5

Entry

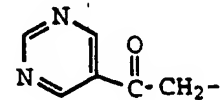
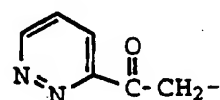
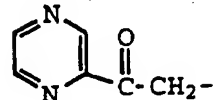
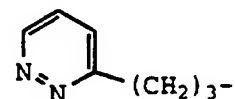
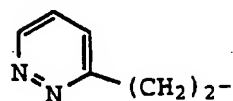
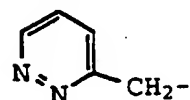
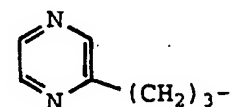
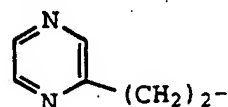
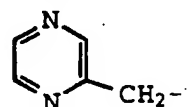
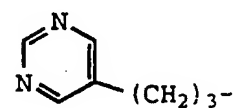
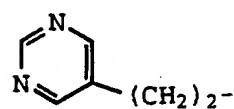
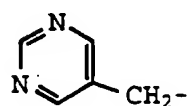
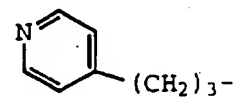
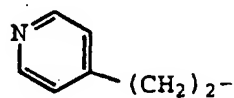
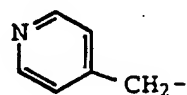
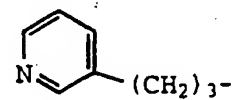
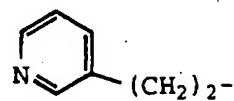
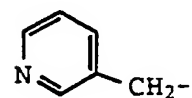
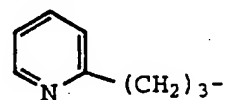
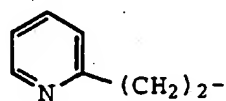
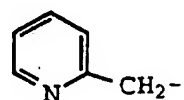
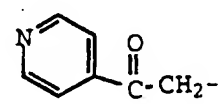
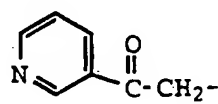
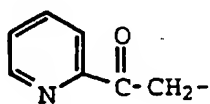
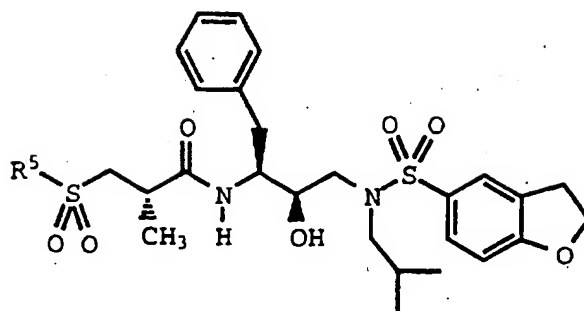
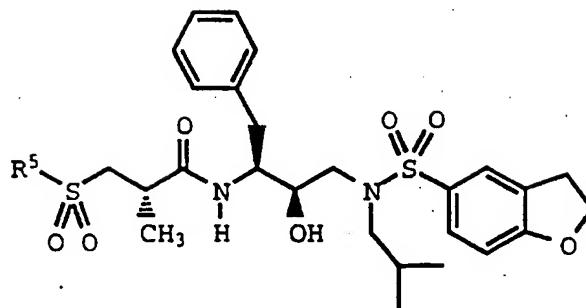
R⁵

TABLE 5E



| 5 | Entry | R ⁵ |
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TABLE 5F



5

Entry

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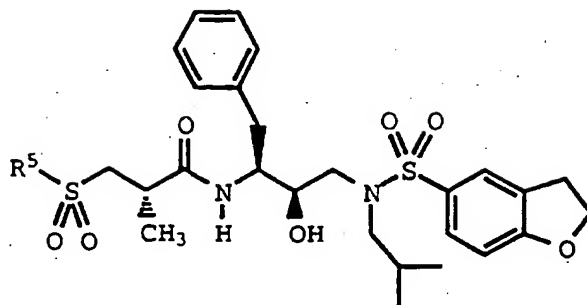
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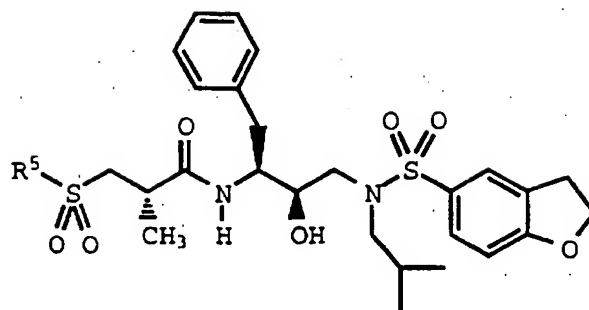
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TABLE 5G



| 5 | Entry | R ⁵ |
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TABLE 5H



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Entry

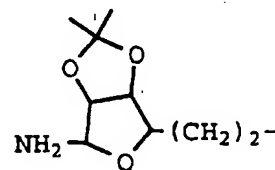
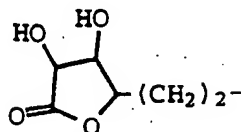
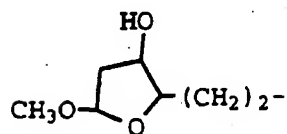
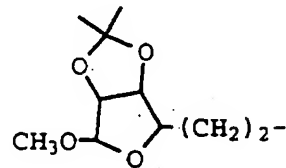
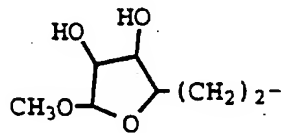
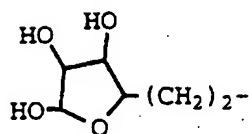
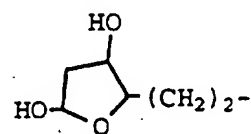
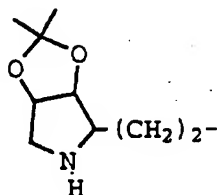
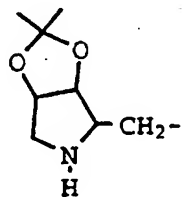
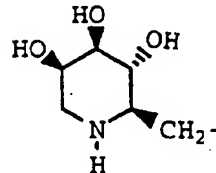
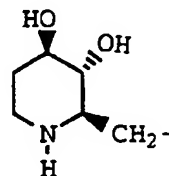
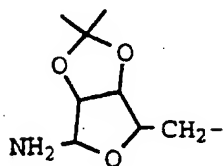
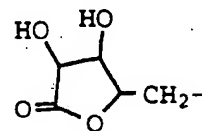
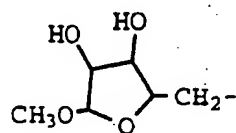
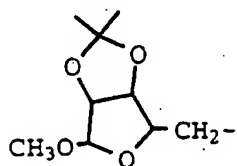
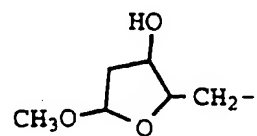
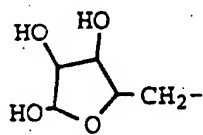
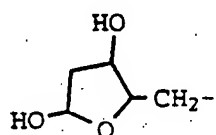
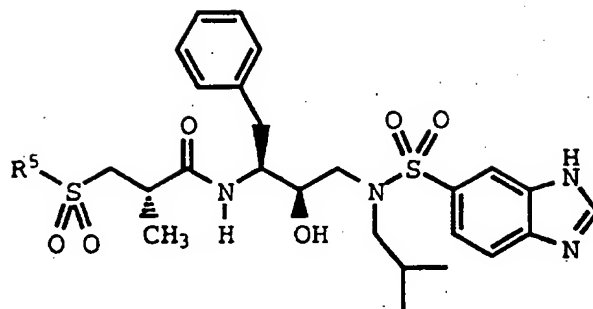
R⁵

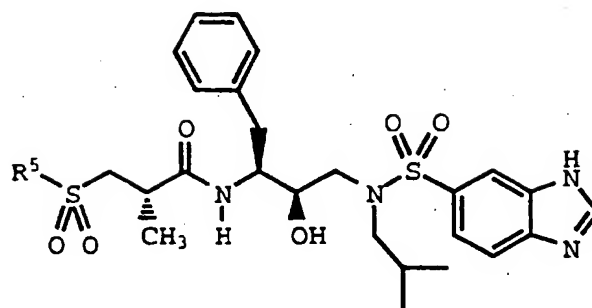
TABLE 6A



5 Entry R⁵

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TABLE 6B



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Entry

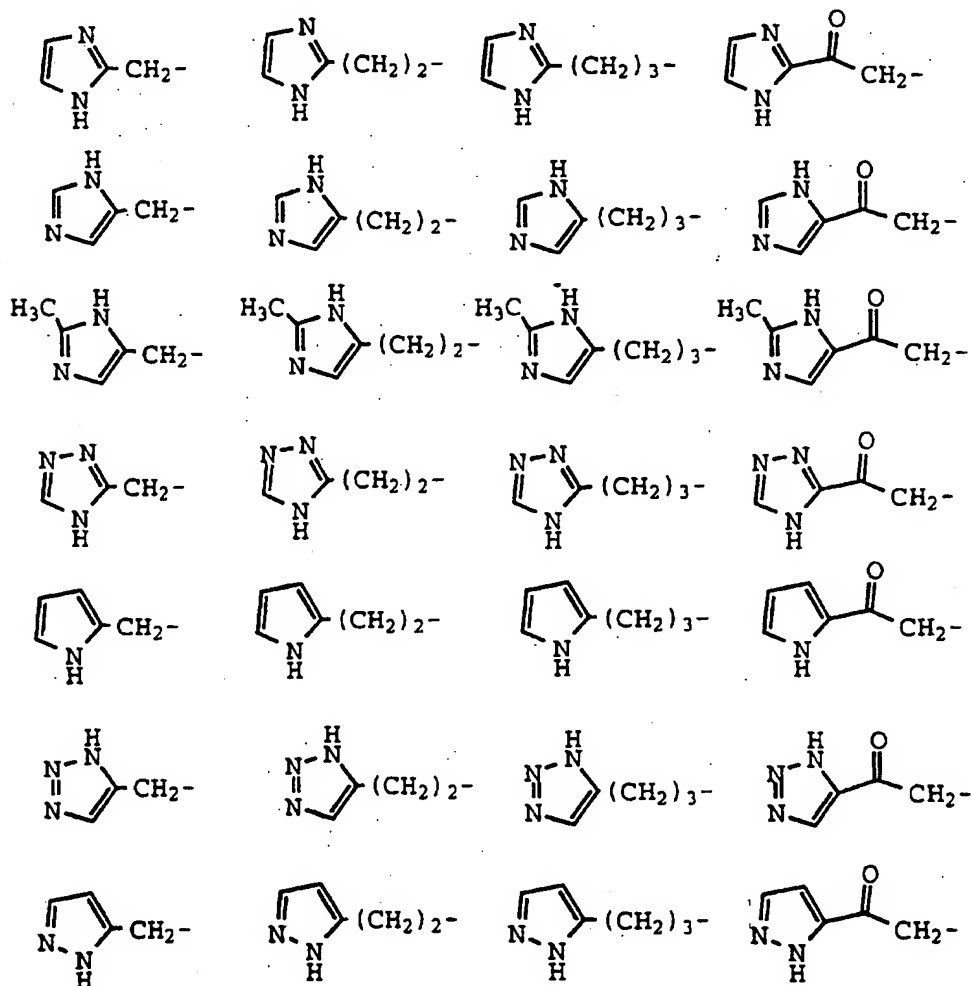
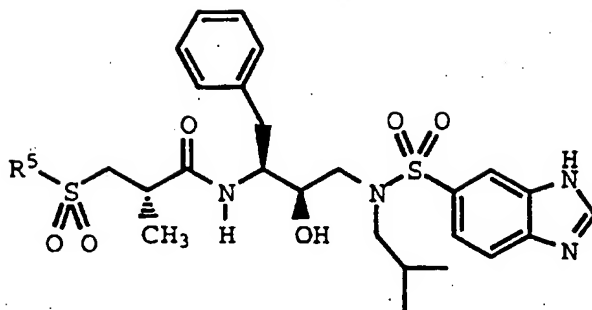
R⁵

TABLE 6C



5

Entry

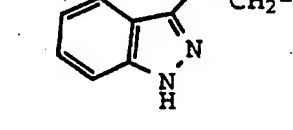
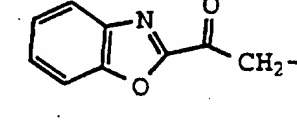
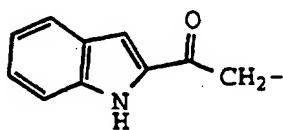
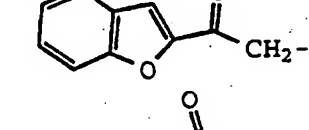
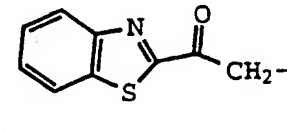
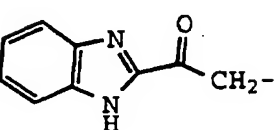
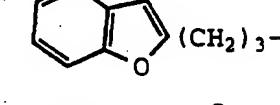
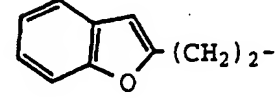
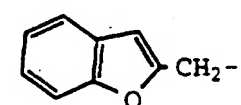
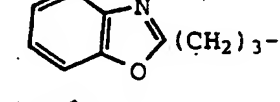
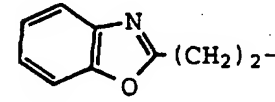
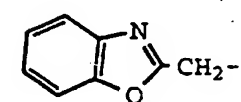
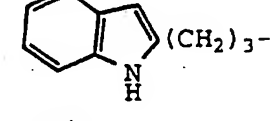
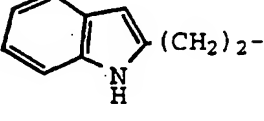
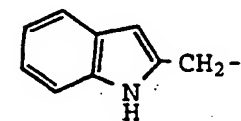
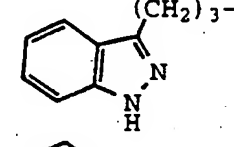
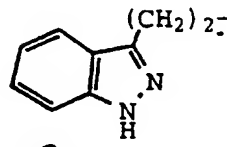
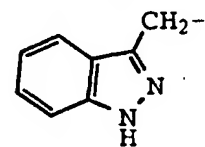
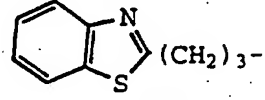
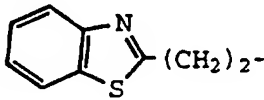
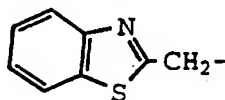
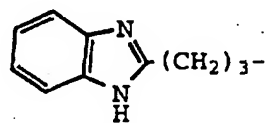
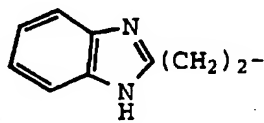
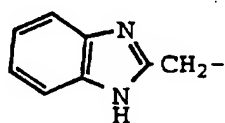
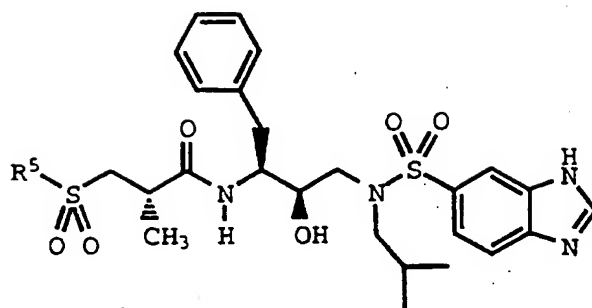
R⁵

TABLE 6D



5

Entry

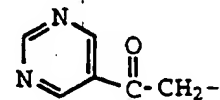
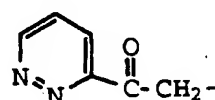
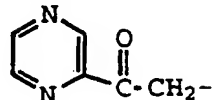
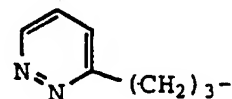
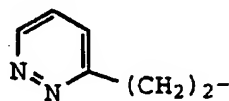
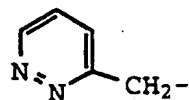
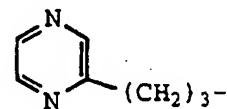
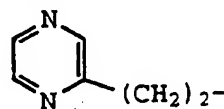
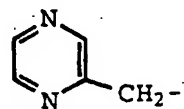
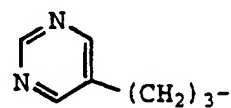
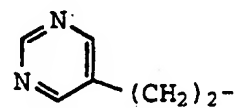
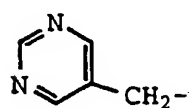
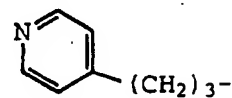
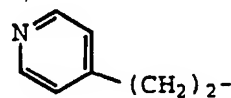
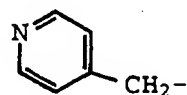
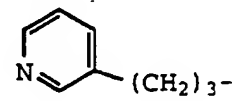
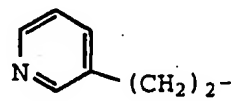
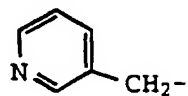
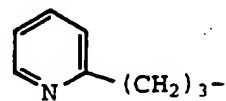
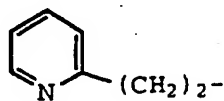
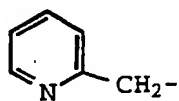
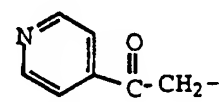
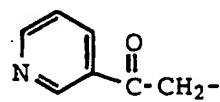
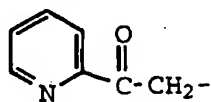
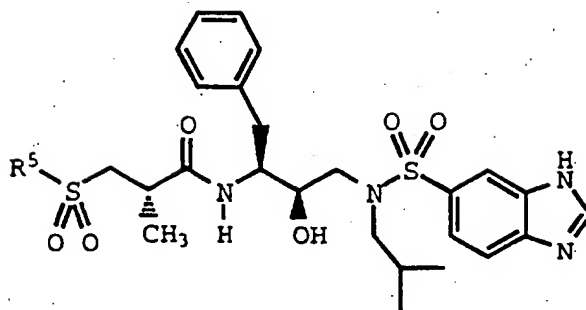
R⁵

TABLE 6E



5

Entry

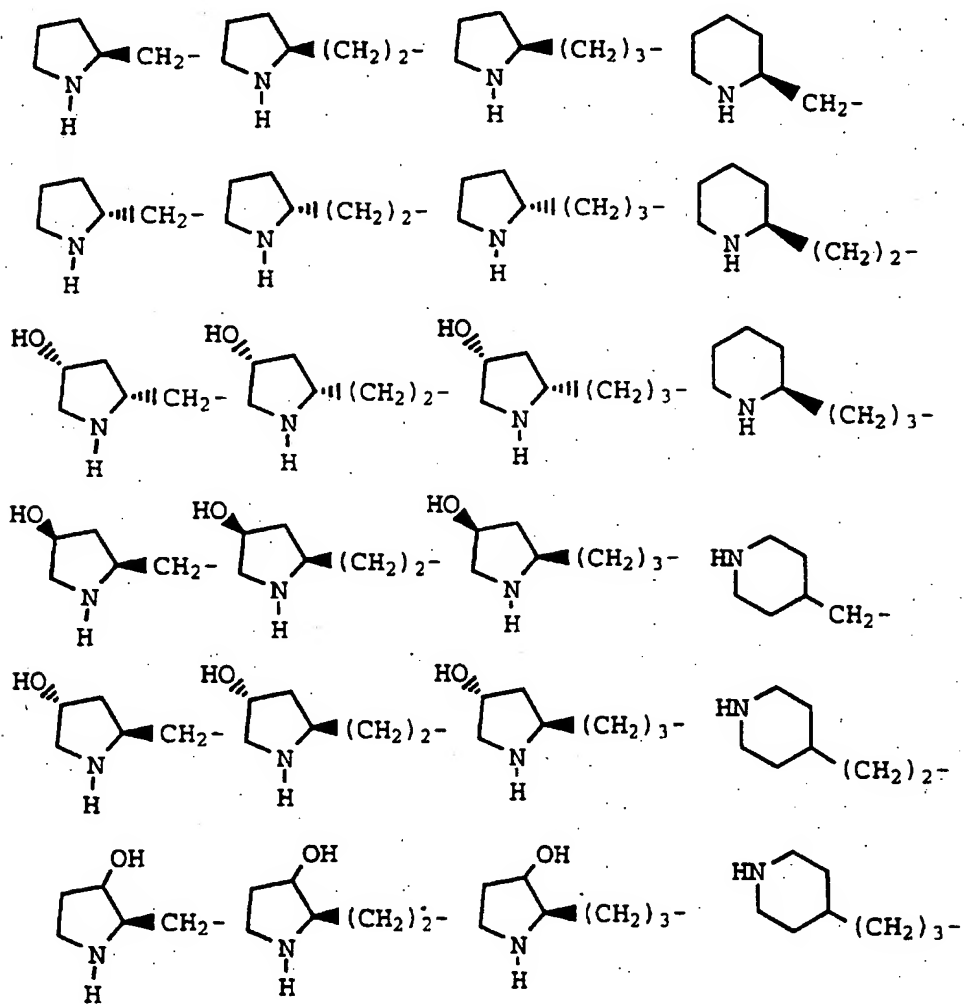
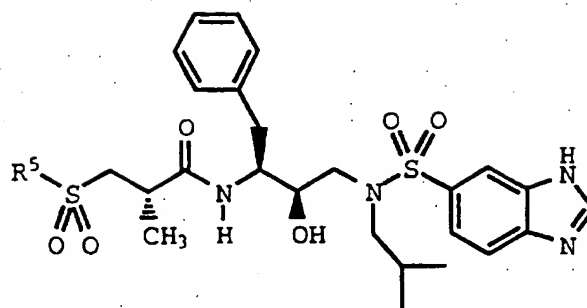
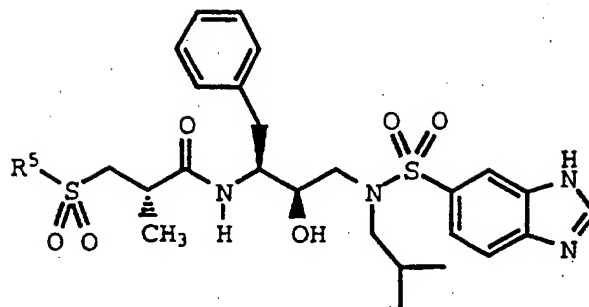
R⁵

TABLE 6F



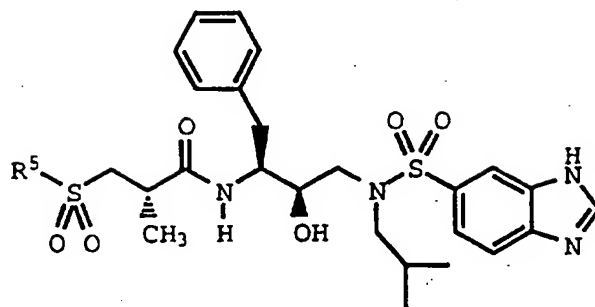
| 5 | Entry | R ⁵ | | |
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TABLE 6G



| 5 | Entry | R ⁵ |
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TABLE 6H



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Entry

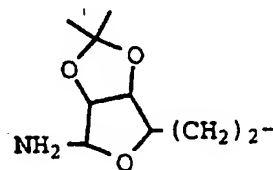
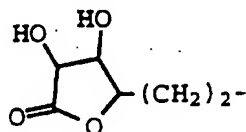
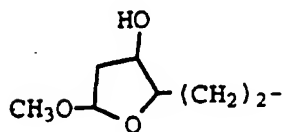
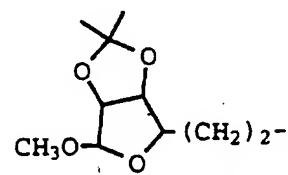
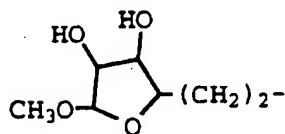
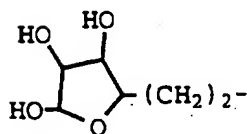
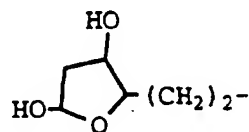
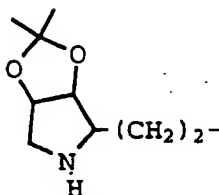
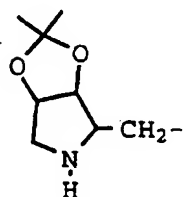
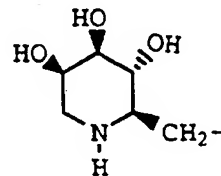
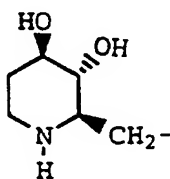
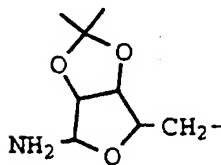
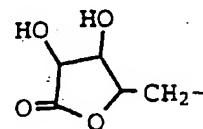
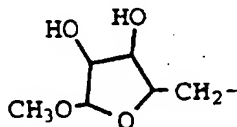
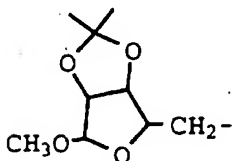
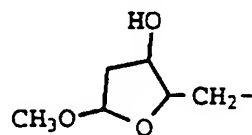
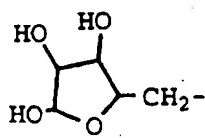
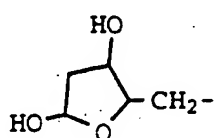
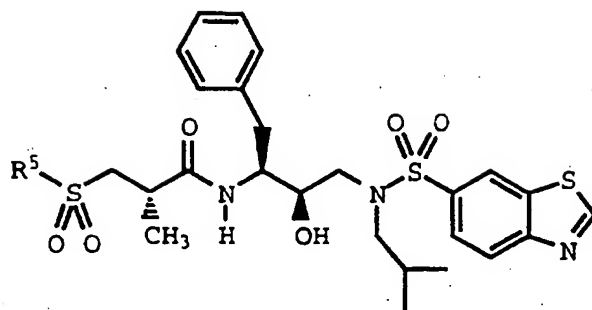
R⁵

TABLE 7A



5

Entry

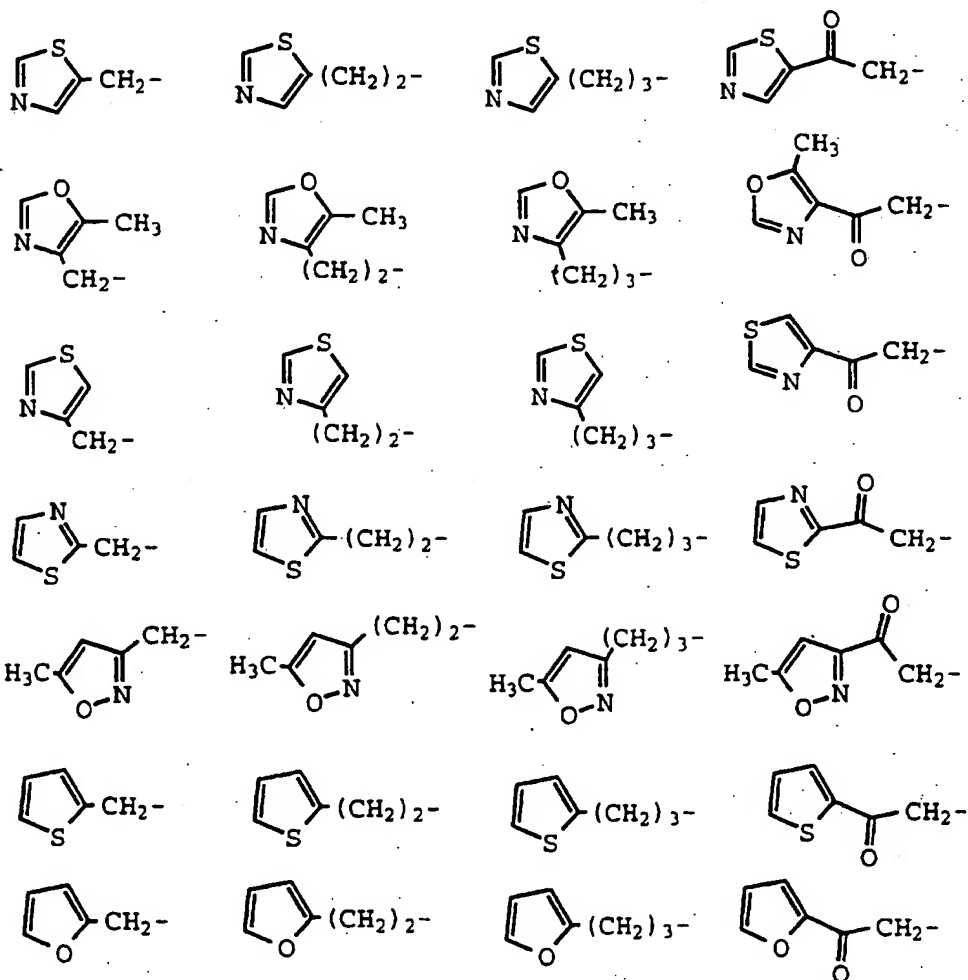
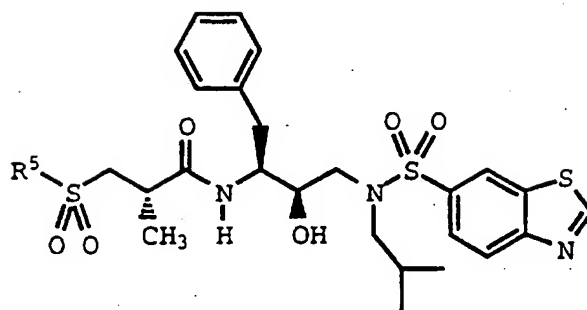
R⁵

TABLE 7B



5

Entry

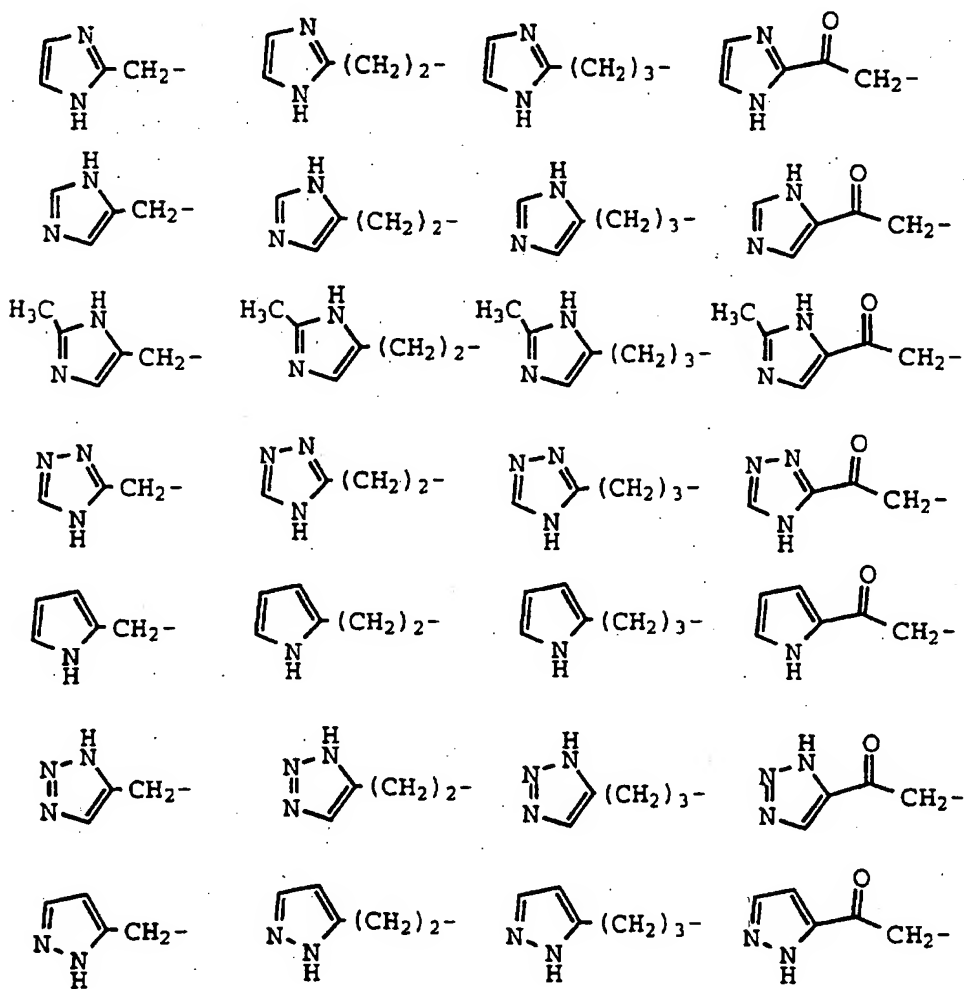
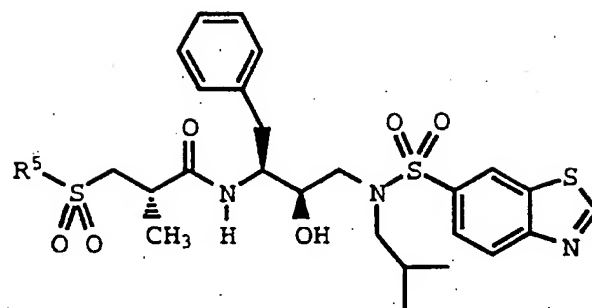
R⁵

TABLE 7C



5

Entry

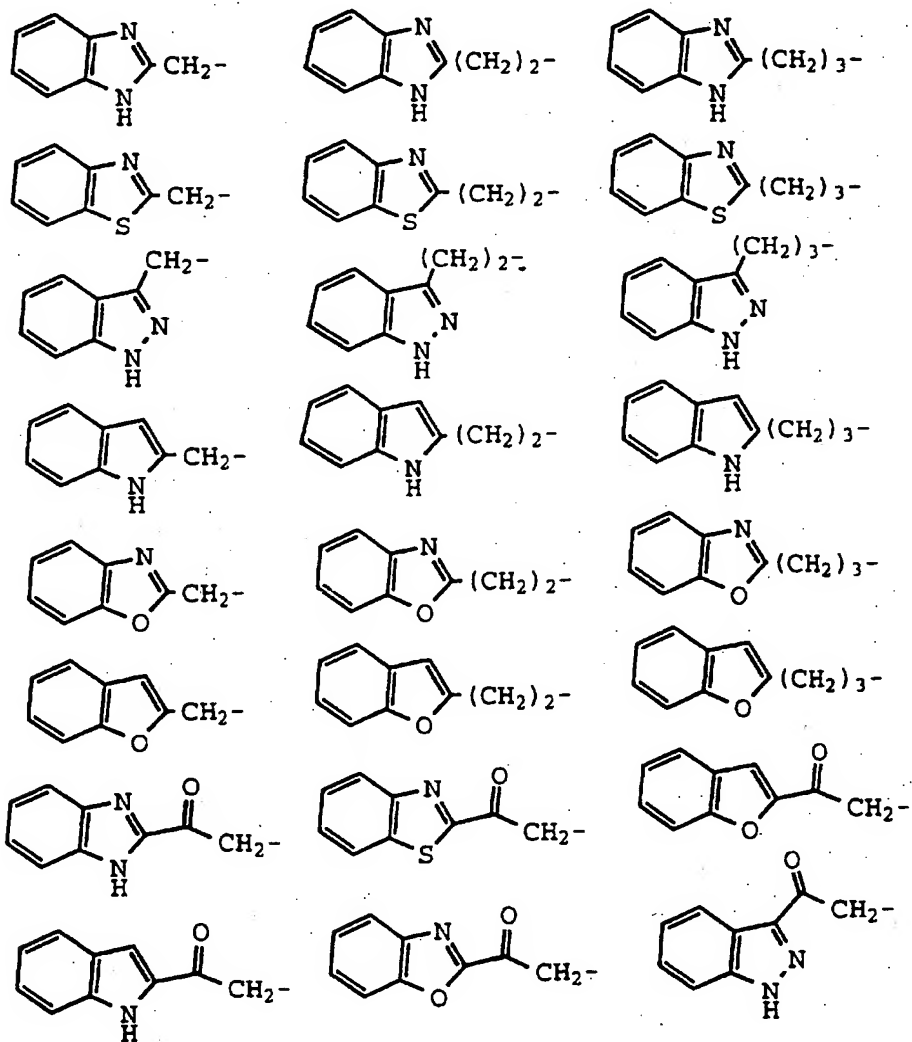
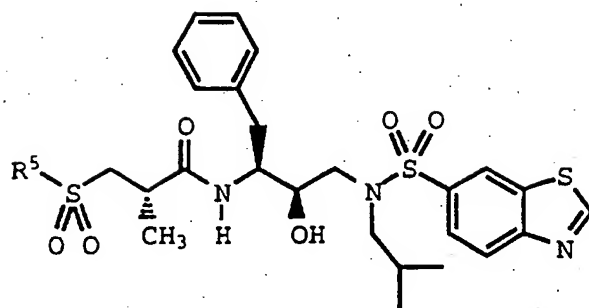
R⁵

TABLE 7D



5

Entry

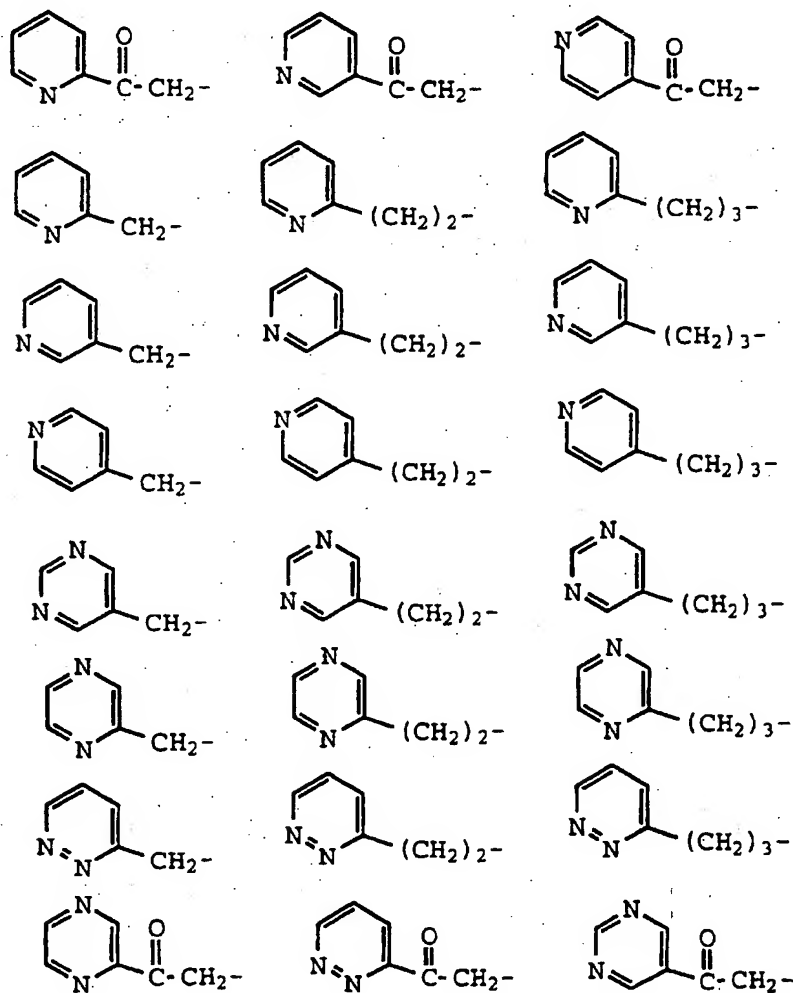
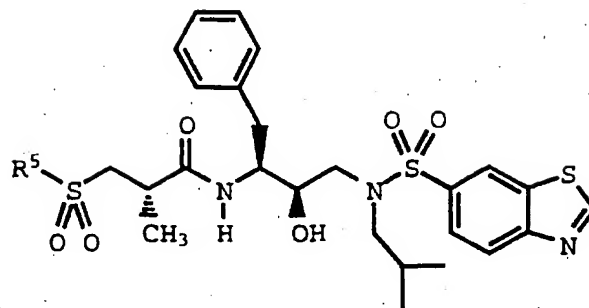
R⁵

TABLE 7E



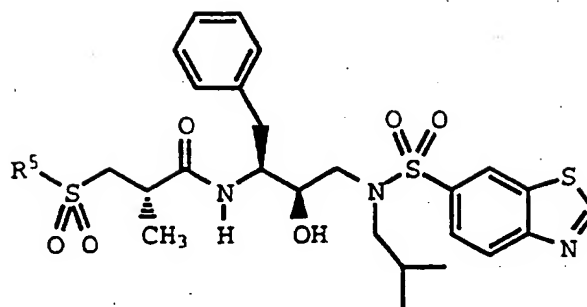
5

Entry

R⁵

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TABLE 7F



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Entry

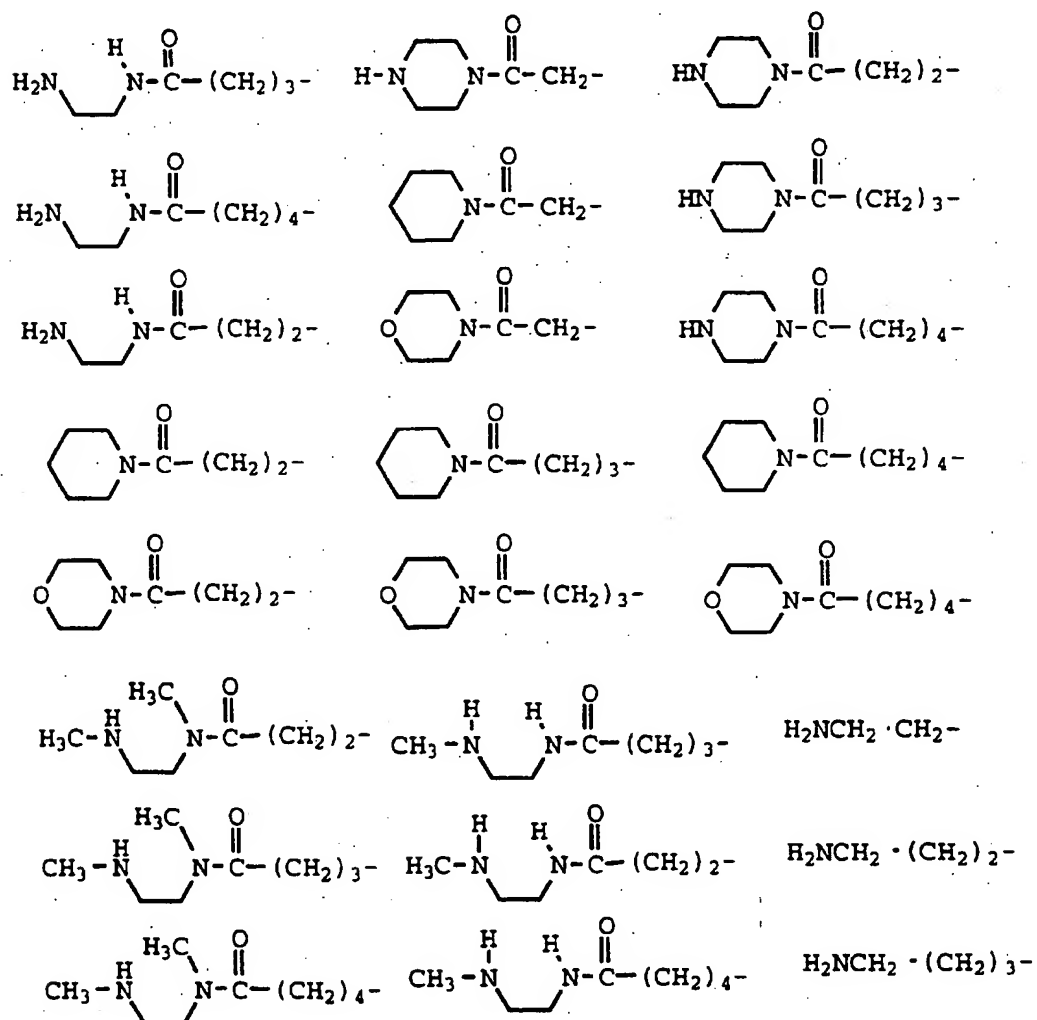
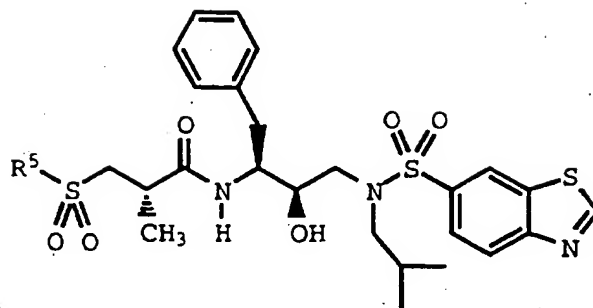
R⁵

TABLE 7G



| 5 | Entry | R ⁵ |
|---|-------|----------------|
|---|-------|----------------|

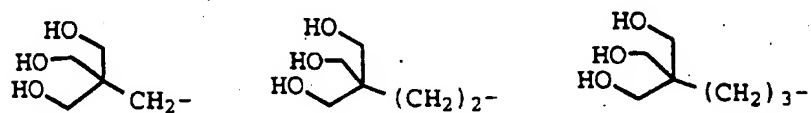
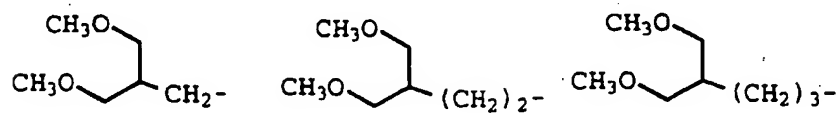
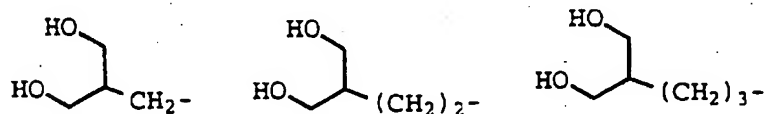
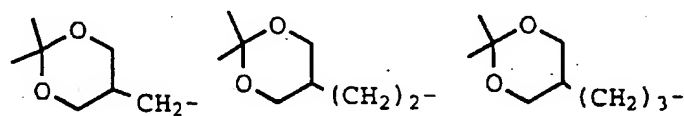
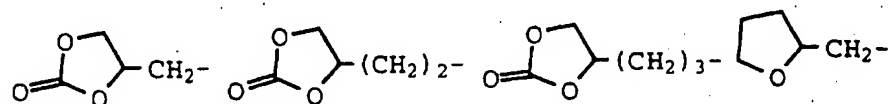
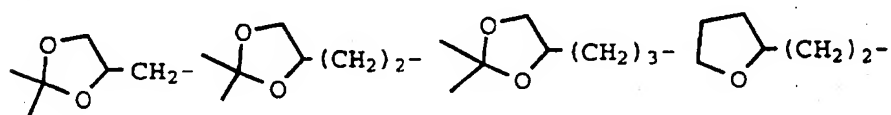
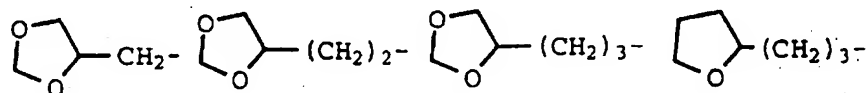
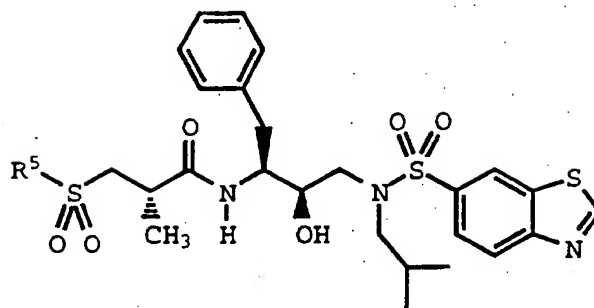


TABLE 7H



5

Entry

R⁵

OC[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

OC[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

OC[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

OC[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

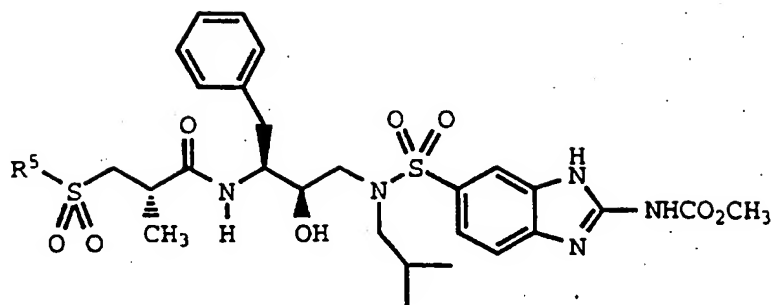
CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

CO[C@H]1O[C@H](CO)[C@@H](O)[C@H]1O

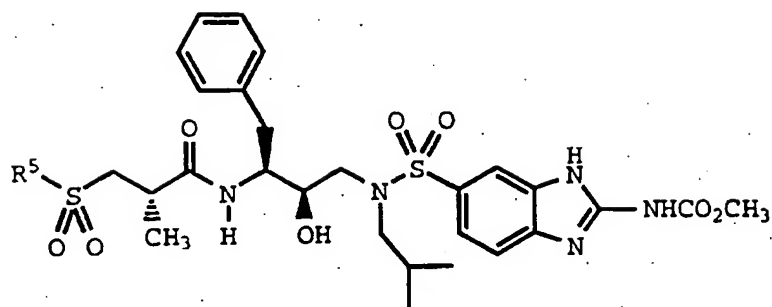
TABLE 8A



5 **Entry** **R⁵**

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TABLE 8B



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Entry

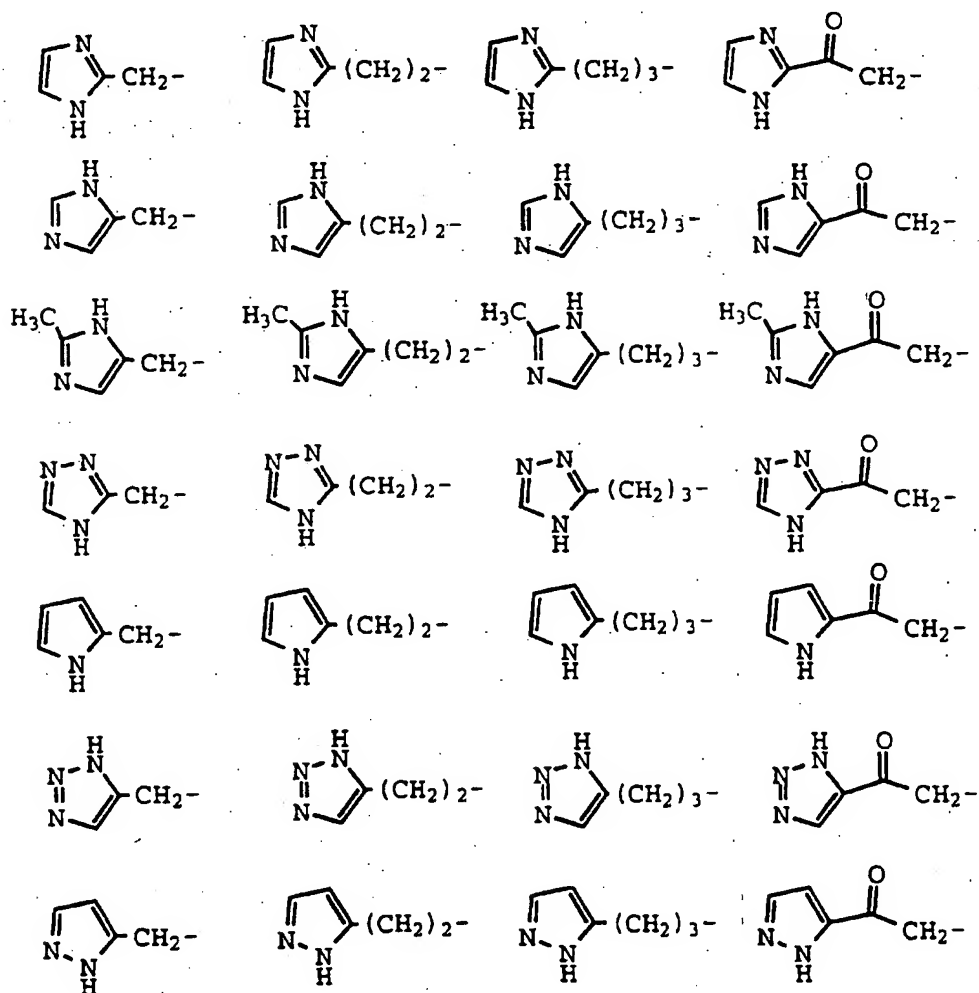
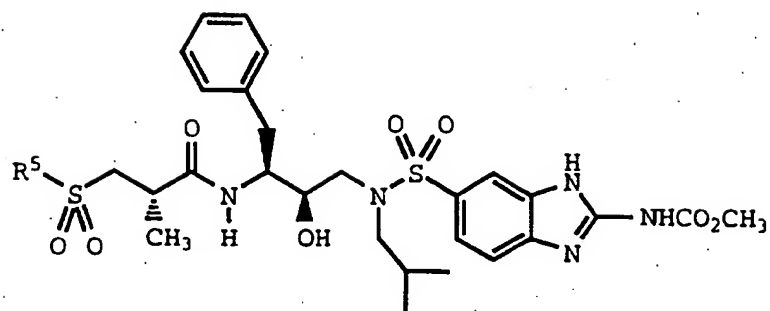
R⁵

TABLE 8C



5

Entry

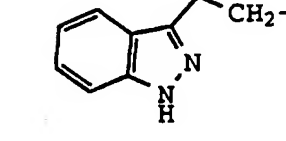
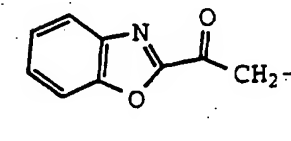
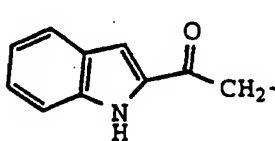
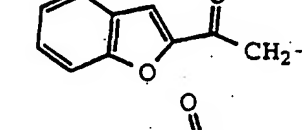
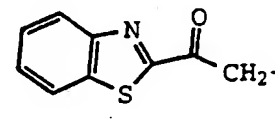
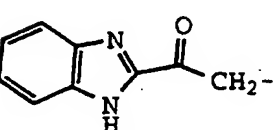
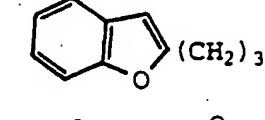
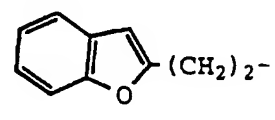
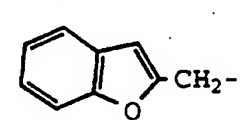
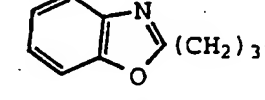
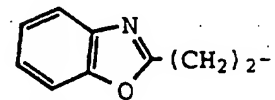
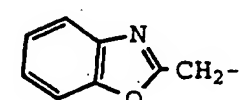
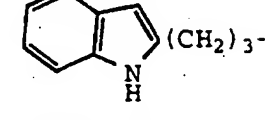
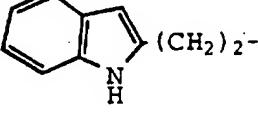
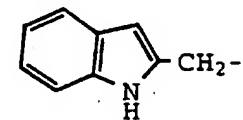
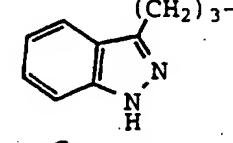
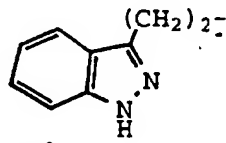
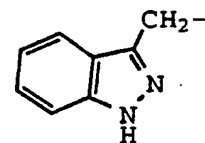
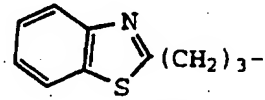
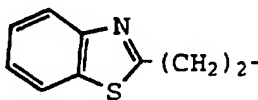
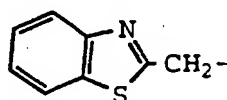
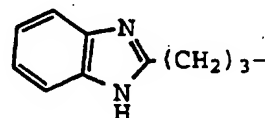
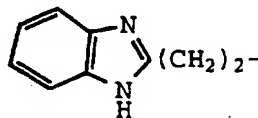
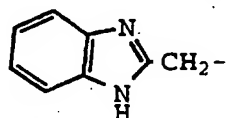
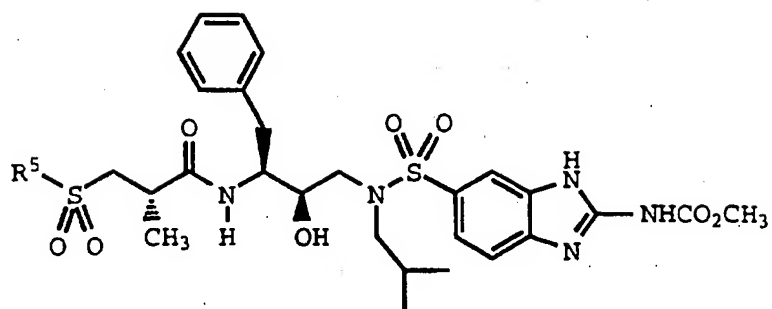
R⁵

TABLE 8D



| 5 | Entry | R ⁵ |
|---|-------|----------------|
|---|-------|----------------|

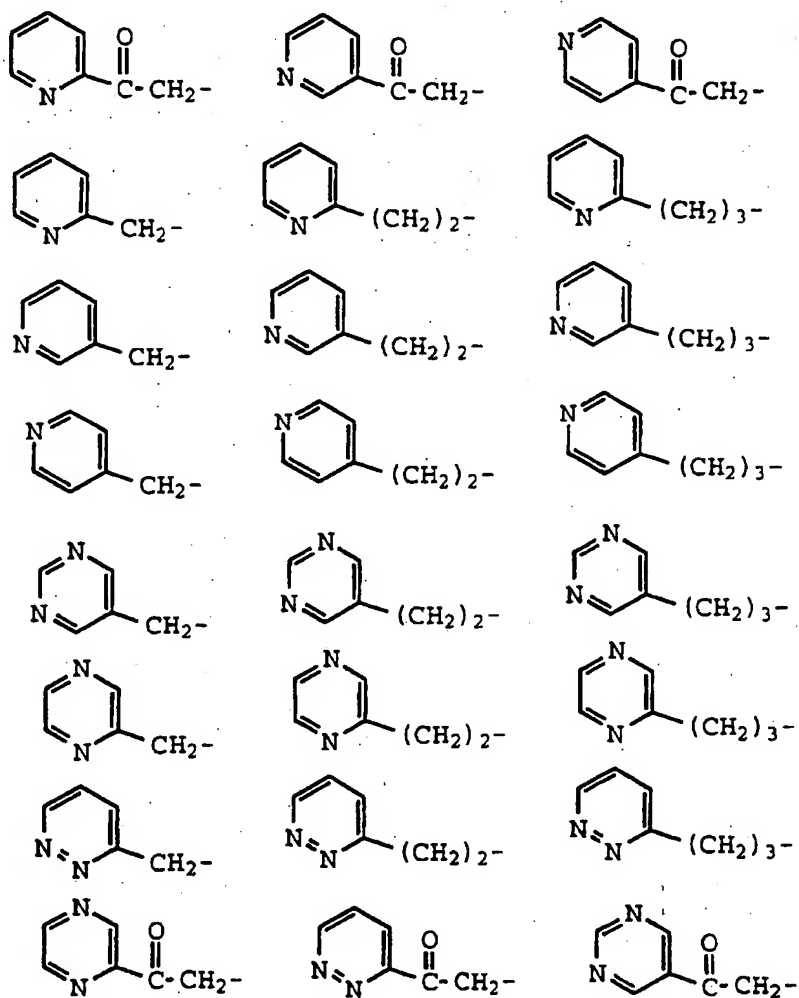
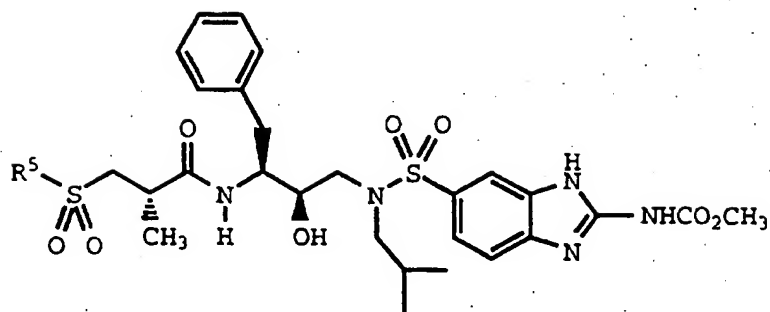
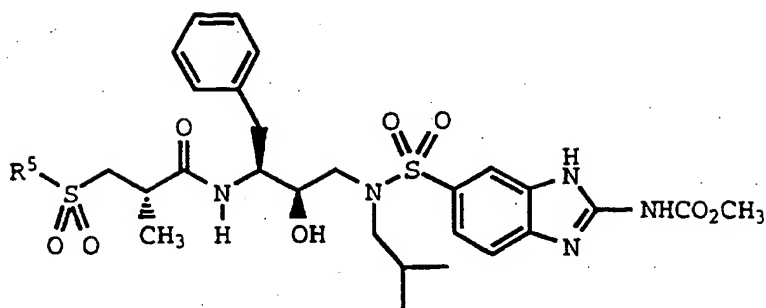


TABLE 8E



| 5 | Entry | R ⁵ |
|---|-------|----------------|
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| | | |
| | | |
| | | |
| | | |

TABLE 8F



5

Entry

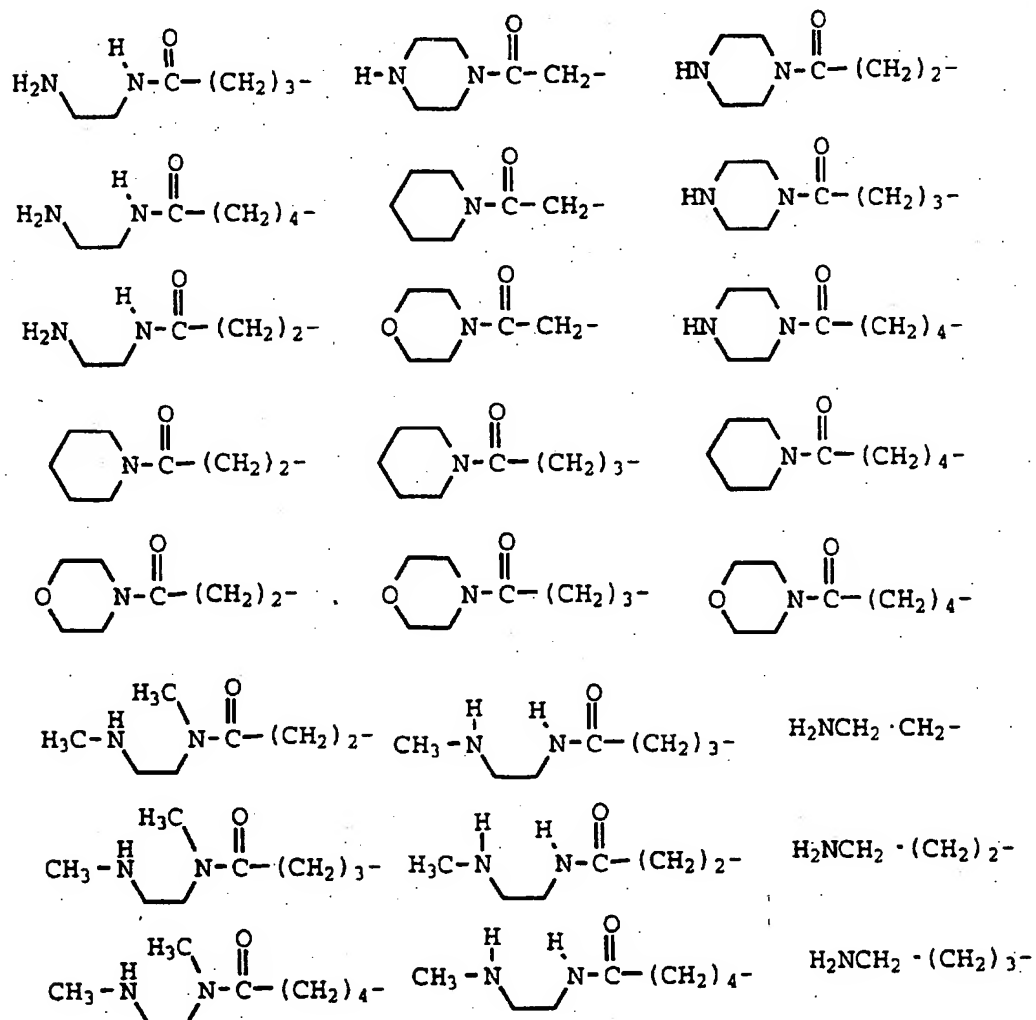
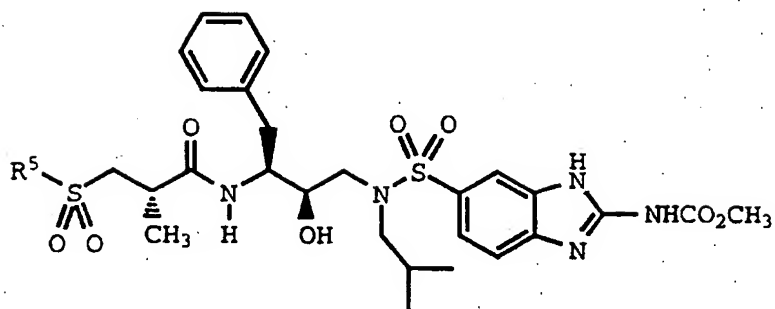
R⁵

TABLE 8G



5

Entry

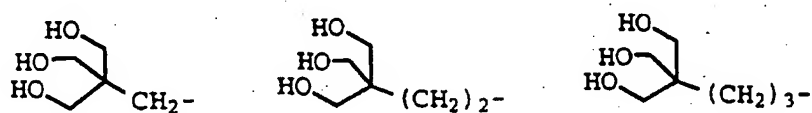
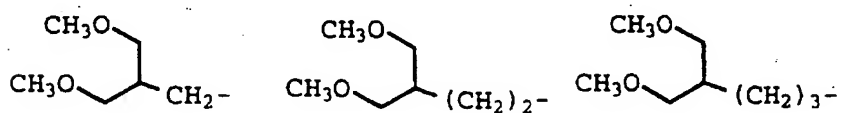
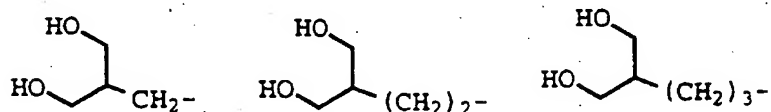
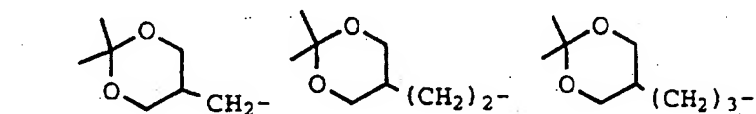
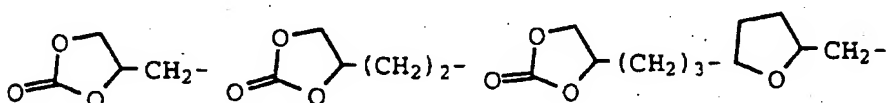
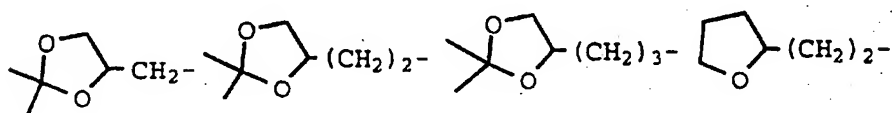
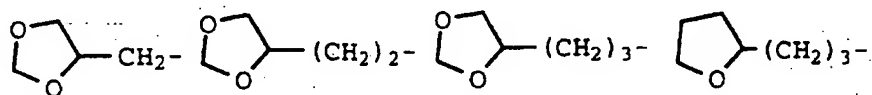
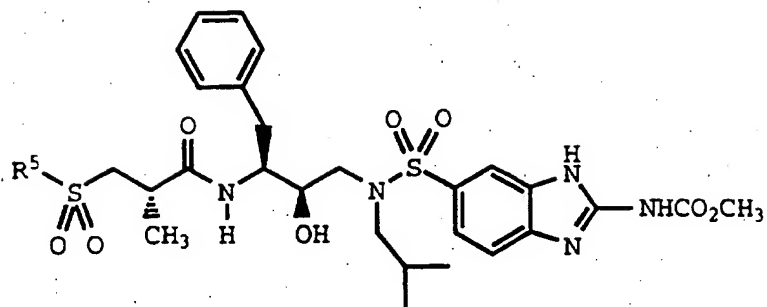
R⁵

TABLE 8H



5

Entry

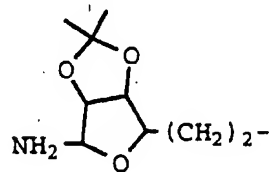
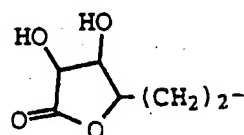
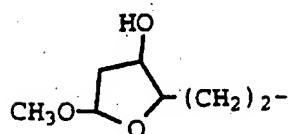
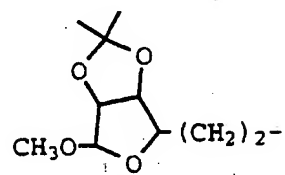
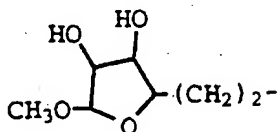
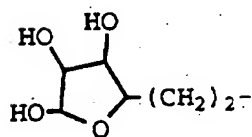
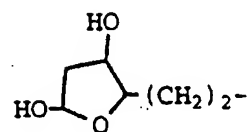
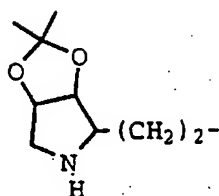
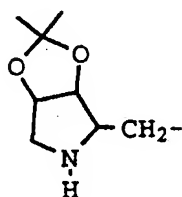
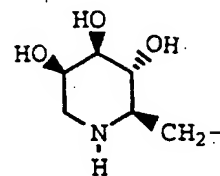
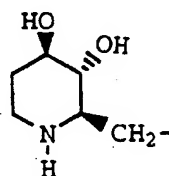
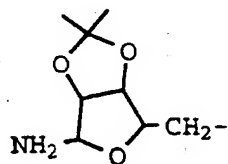
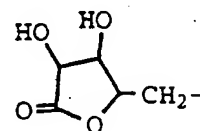
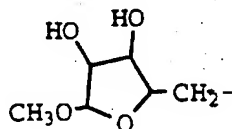
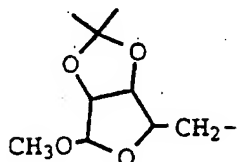
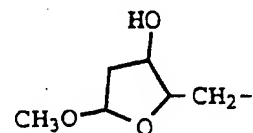
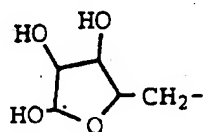
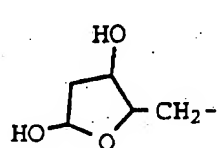
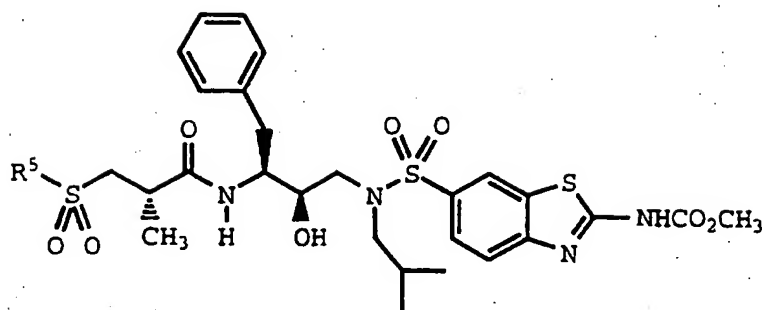
R⁵

TABLE 9A



5 Entry

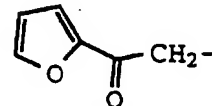
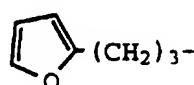
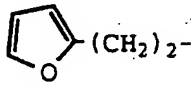
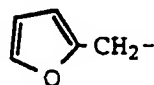
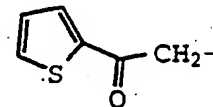
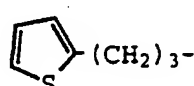
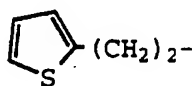
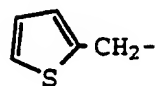
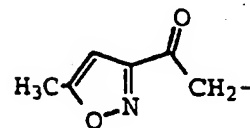
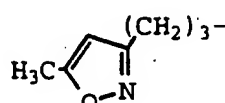
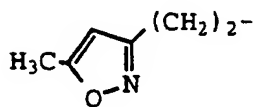
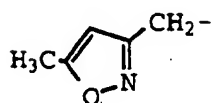
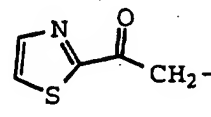
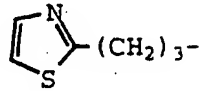
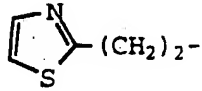
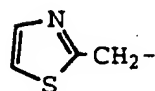
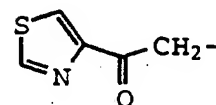
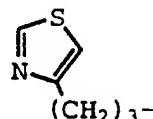
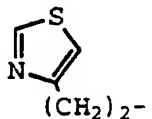
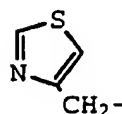
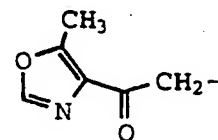
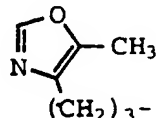
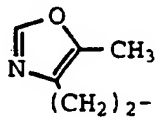
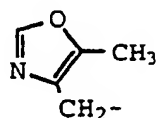
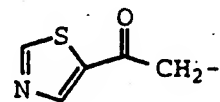
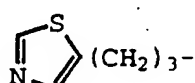
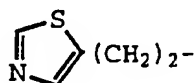
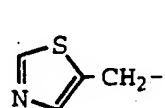
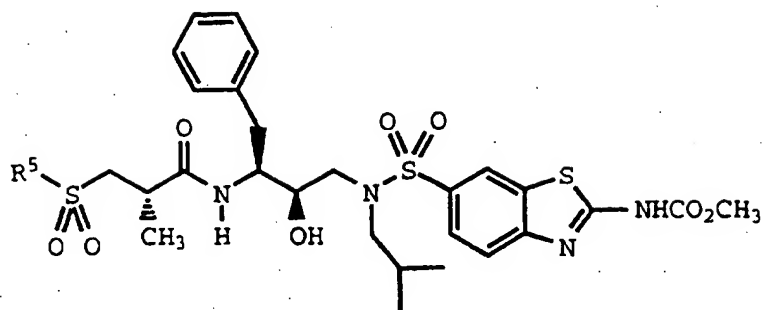
R⁵

TABLE 9B



5

Entry

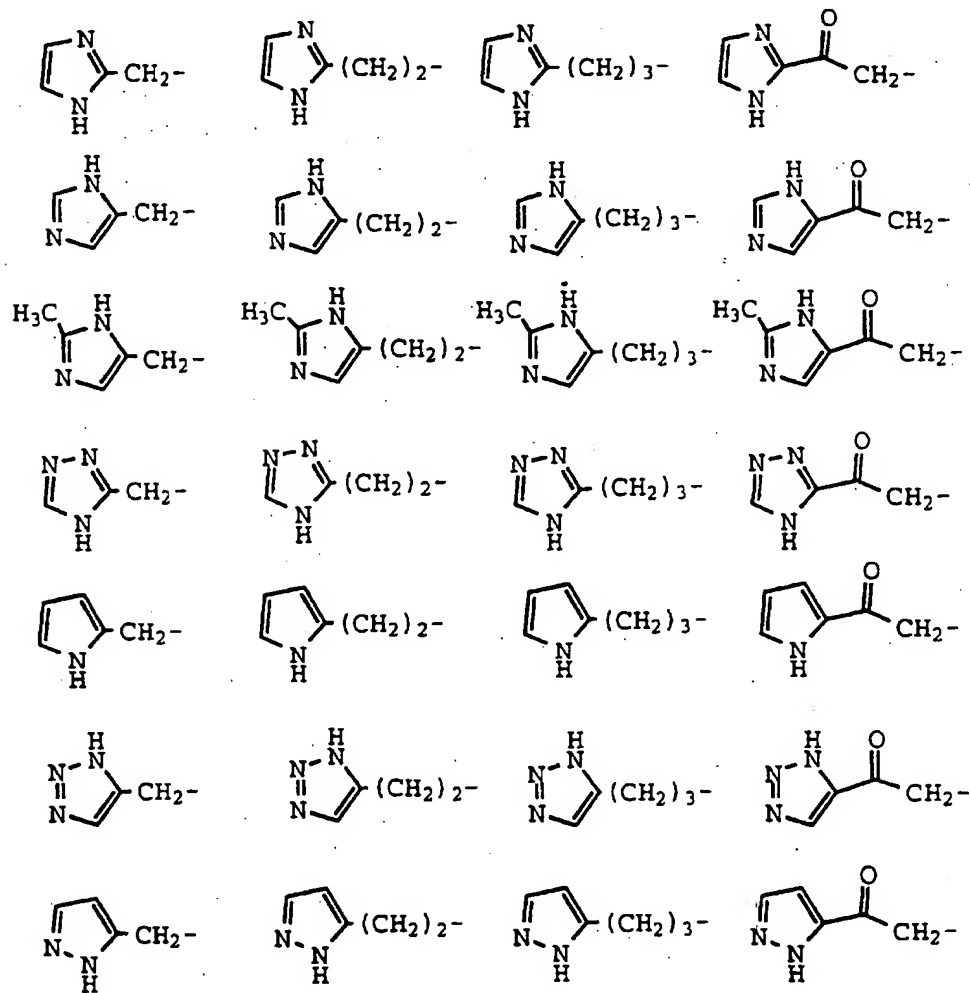
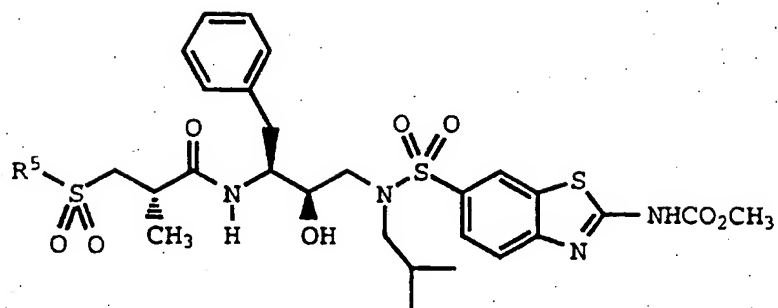
R⁵

TABLE 9C



5

Entry

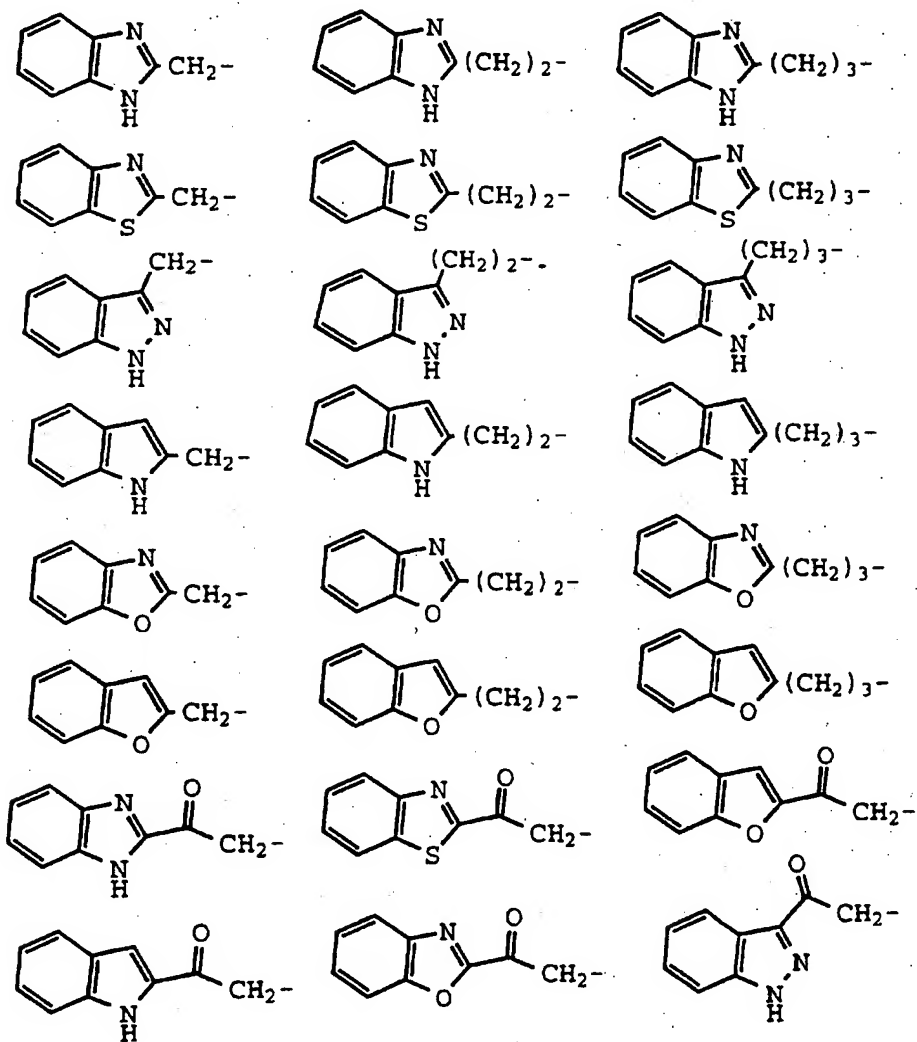
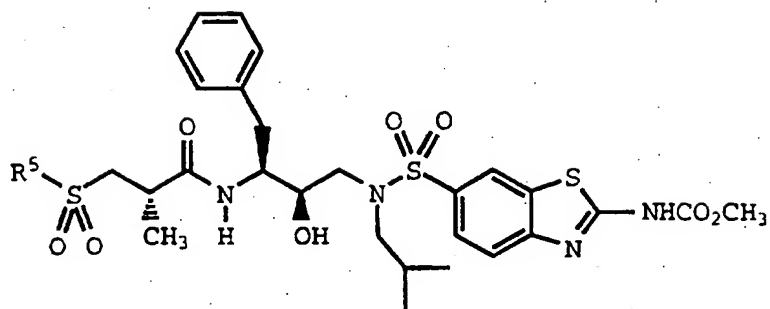
R⁵

TABLE 9D



5

Entry

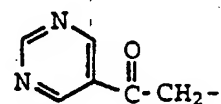
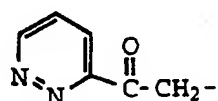
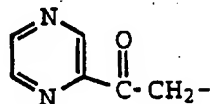
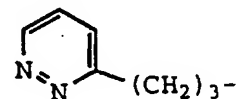
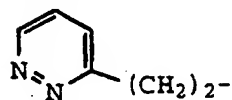
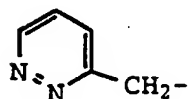
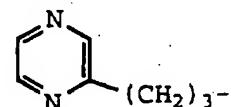
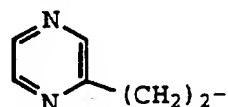
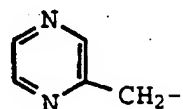
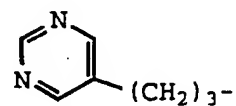
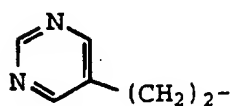
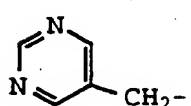
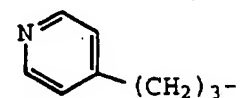
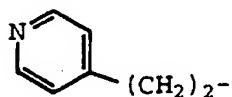
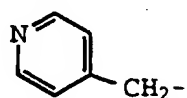
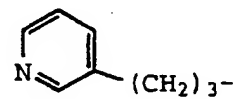
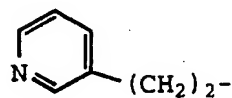
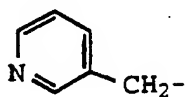
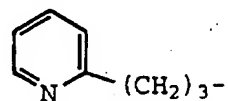
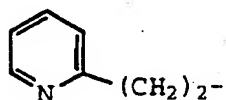
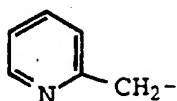
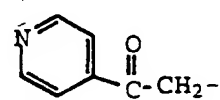
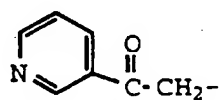
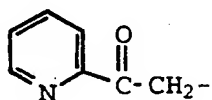
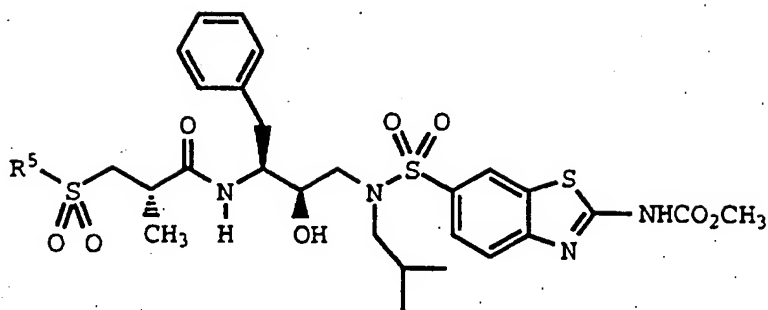
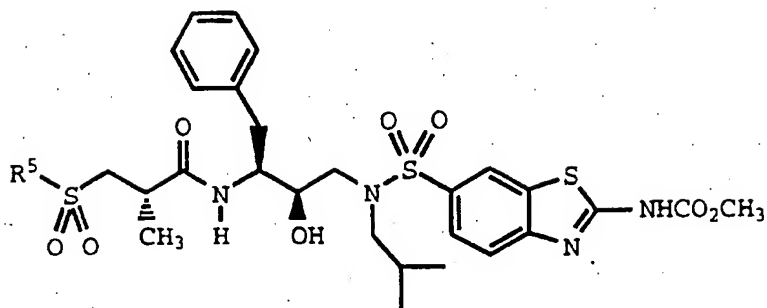
R⁵

TABLE 9E



| 5 | Entry | R ⁵ |
|---|-------|----------------|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

TABLE 9F



5

Entry

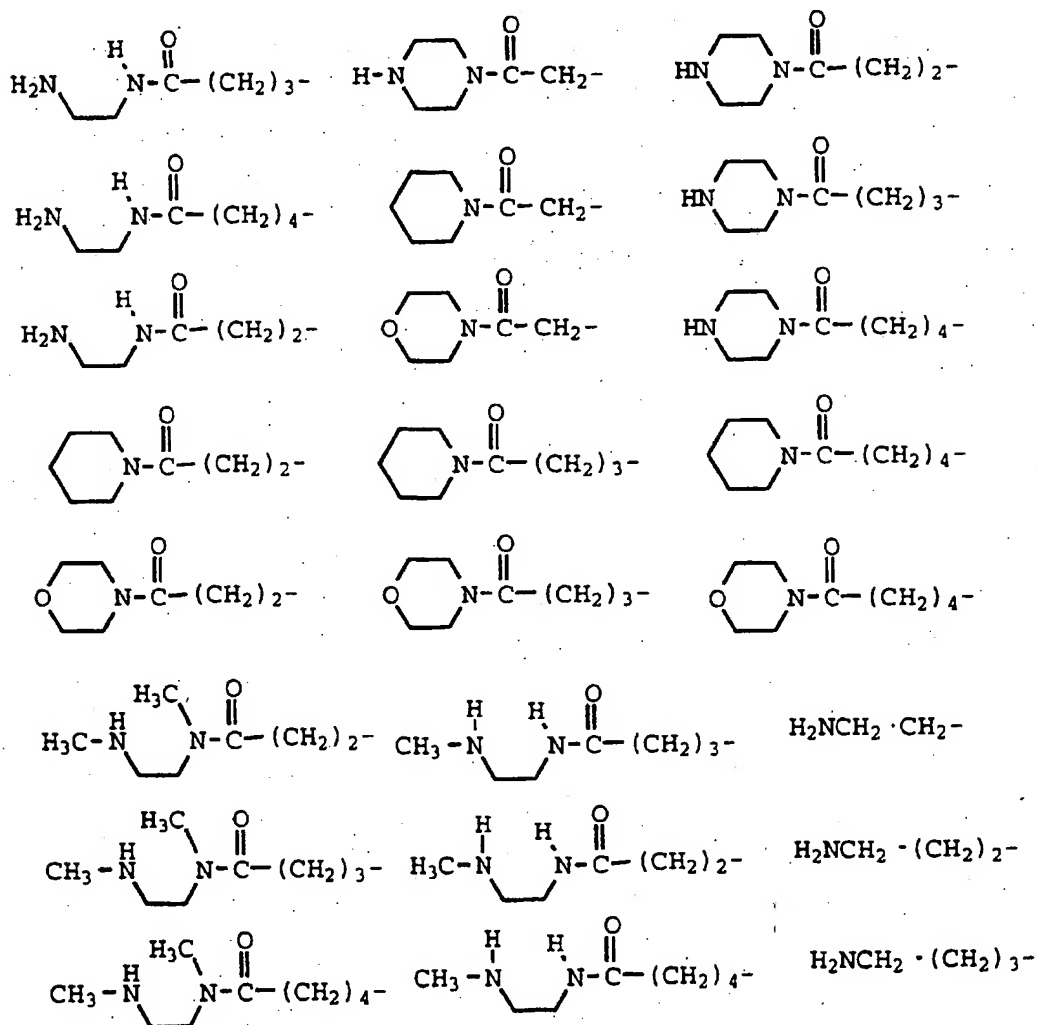
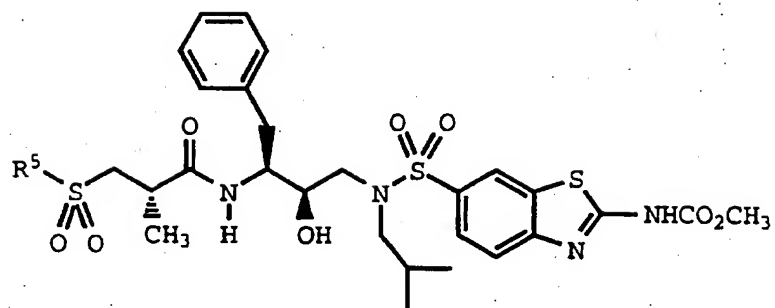
R⁵

TABLE 9G



| 5 | Entry | R ⁵ |
|---|-------|----------------|
|---|-------|----------------|

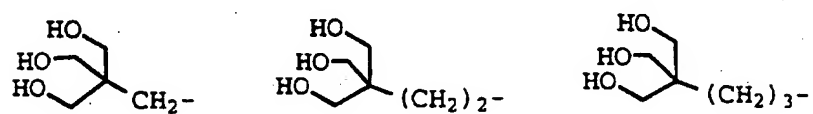
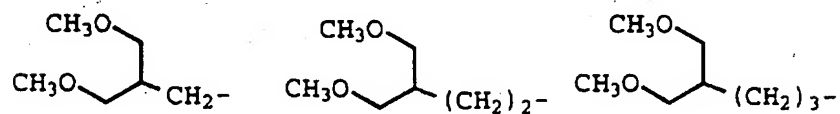
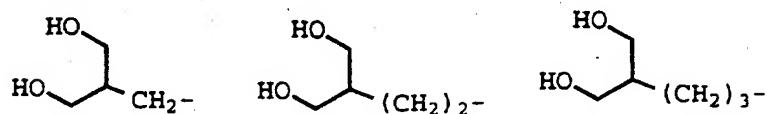
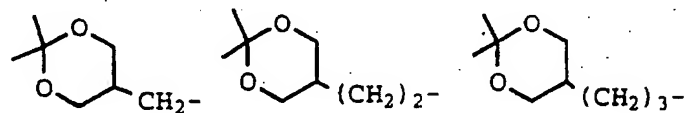
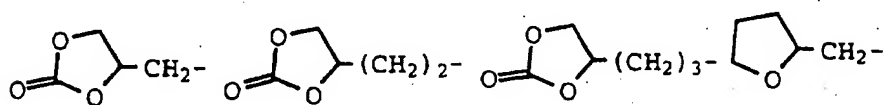
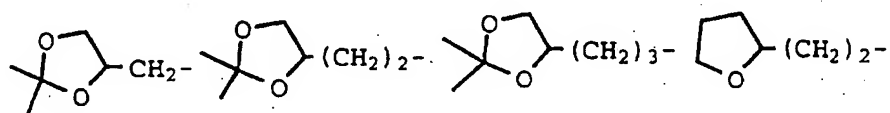
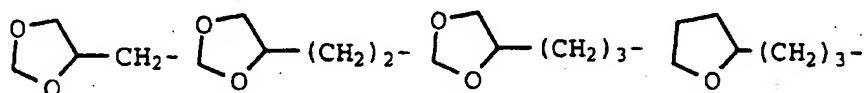
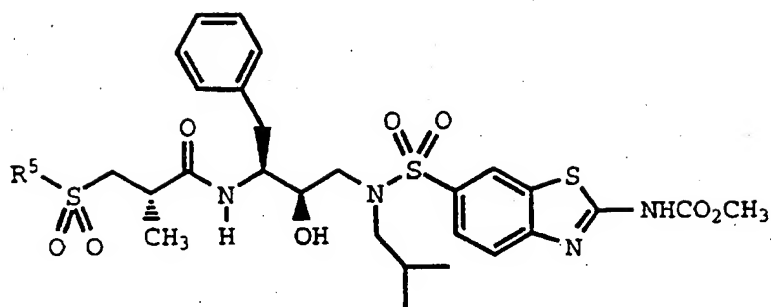


TABLE 9H



5

Entry

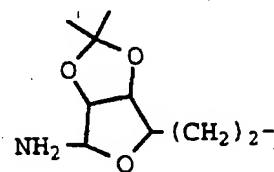
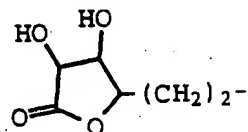
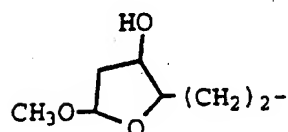
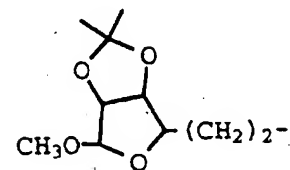
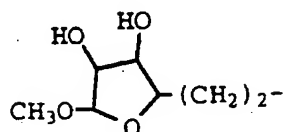
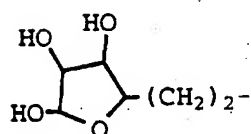
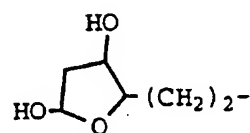
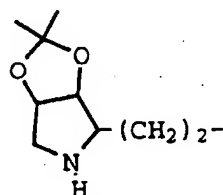
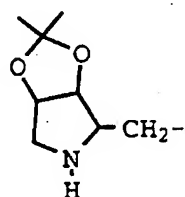
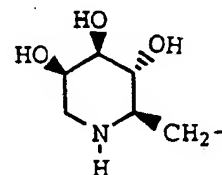
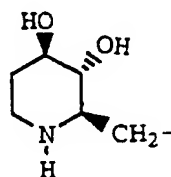
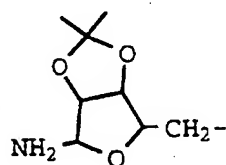
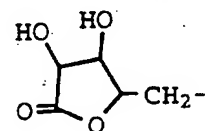
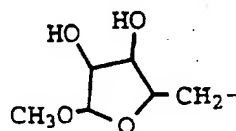
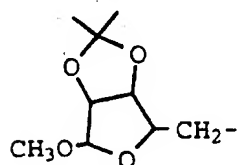
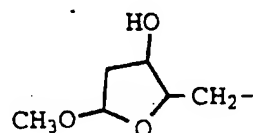
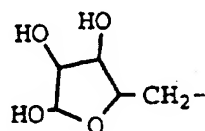
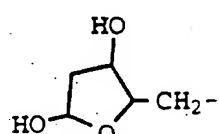
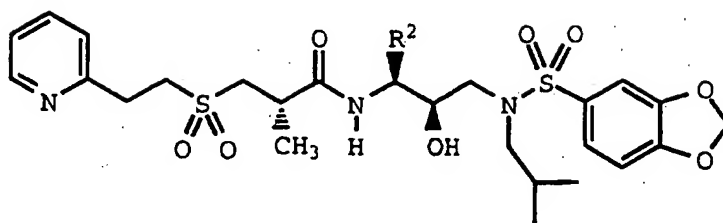
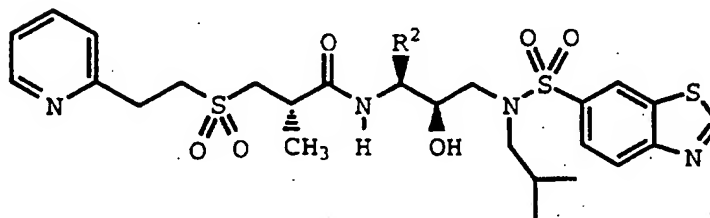
R⁵

TABLE 10A



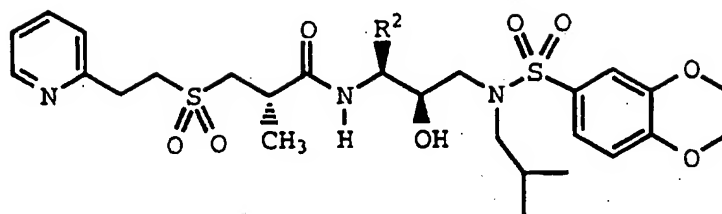
| 5 | Entry | R ² |
|----|--|--|
| | (CH ₃) ₂ CHCH ₂ - | (4-FC ₆ H ₅)CH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - | (naphth-2-yl)CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ CH ₂ - | C ₆ H ₅ SCH ₂ - |
| 10 | (4-CH ₃ OC ₆ H ₅)CH ₂ - | (naphth-2-yl)SCH ₂ - |

TABLE 10B



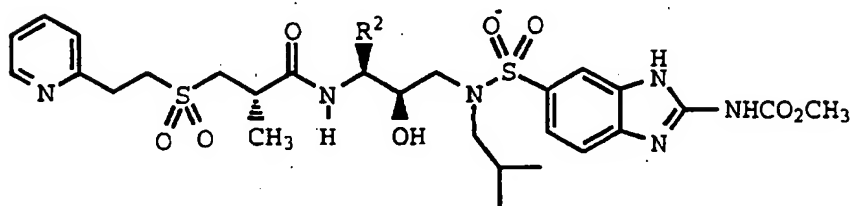
| 15 | Entry | R ² |
|----|--|--|
| | (CH ₃) ₂ CHCH ₂ - | (4-FC ₆ H ₅)CH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - | (naphth-2-yl)CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ CH ₂ - | C ₆ H ₅ SCH ₂ - |
| 20 | (4-CH ₃ OC ₆ H ₅)CH ₂ - | (naphth-2-yl)SCH ₂ - |

TABLE 10C



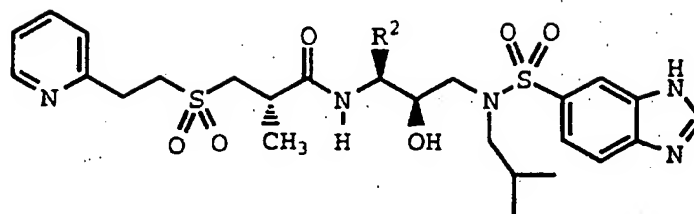
| Entry | R ² | |
|-------|--|--|
| 5 | (CH ₃) ₂ CHCH ₂ - | (4-FC ₆ H ₅)CH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - | (naphth-2-yl)CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ CH ₂ - | C ₆ H ₅ SCH ₂ - |
| 10 | (4-CH ₃ OC ₆ H ₅)CH ₂ - | (naphth-2-yl)SCH ₂ - |

TABLE 10D



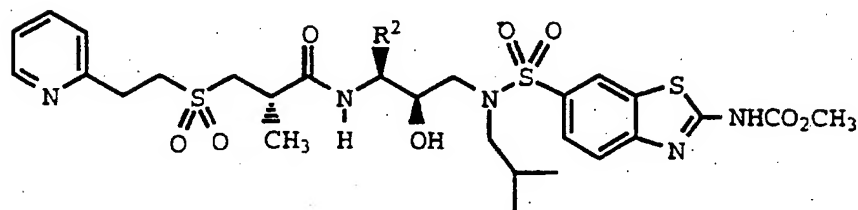
| Entry | R ² | |
|-------|--|--|
| 15 | (CH ₃) ₂ CHCH ₂ - | (4-FC ₆ H ₅)CH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - | (naphth-2-yl)CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ CH ₂ - | C ₆ H ₅ SCH ₂ - |
| 20 | (4-CH ₃ OC ₆ H ₅)CH ₂ - | (naphth-2-yl)SCH ₂ - |

TABLE 10E



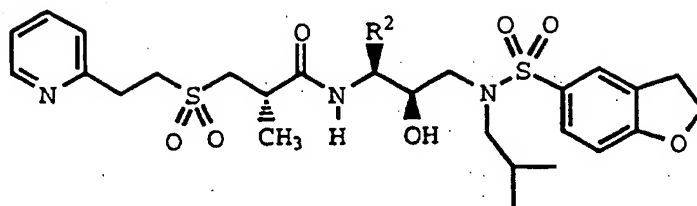
| Entry | R ² |
|-------|--|
| 5 | (CH ₃) ₂ CHCH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - |
| | C ₆ H ₅ CH ₂ - |
| 10 | (4-CH ₃ OC ₆ H ₅)CH ₂ - |
| | (4-FC ₆ H ₅)CH ₂ - |
| | (naphth-2-yl)CH ₂ - |
| | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ SCH ₂ - |
| | (naphth-2-yl)SCH ₂ - |

TABLE 10F

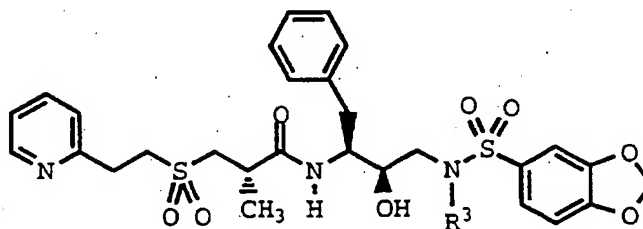


| Entry | R ² |
|-------|--|
| 15 | (CH ₃) ₂ CHCH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - |
| | C ₆ H ₅ CH ₂ - |
| 20 | (4-CH ₃ OC ₆ H ₅)CH ₂ - |
| | (4-FC ₆ H ₅)CH ₂ - |
| | (naphth-2-yl)CH ₂ - |
| | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ SCH ₂ - |
| | (naphth-2-yl)SCH ₂ - |

225

TABLE 10G

| Entry | R ² |
|-------|--|
| | (CH ₃) ₂ CHCH ₂ - |
| | CH ₃ CH ₂ CH ₂ CH ₂ - |
| | CH ₃ SCH ₂ CH ₂ - |
| | C ₆ H ₅ CH ₂ - |
| 10 | (4-CH ₃ OC ₆ H ₅)CH ₂ - |
| | (4-FC ₆ H ₅)CH ₂ - |
| | (naphth-2-yl)CH ₂ - |
| | C ₆ H ₁₁ CH ₂ - |
| | C ₆ H ₅ SCH ₂ - |
| | (naphth-2-yl)SCH ₂ - |

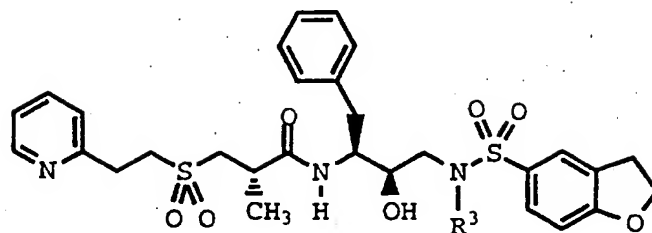
TABLE 11A

15

| Entry | R ³ |
|--|----------------|
| -CH ₂ CH ₂ CH ₃ | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | |
| -CH ₂ CH(CH ₃) ₂ | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | |

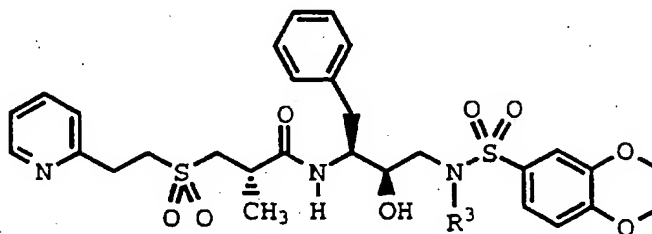
20

TABLE 11B



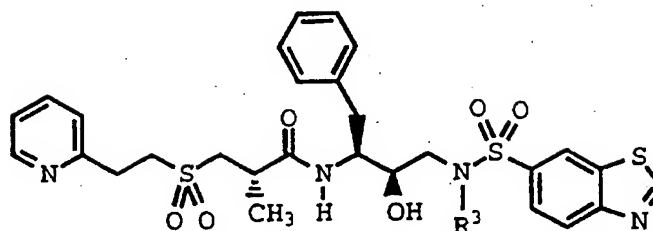
| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 11C



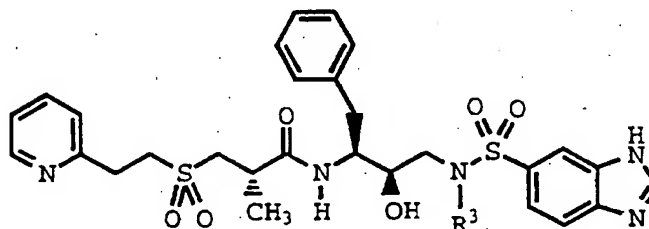
| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 11D



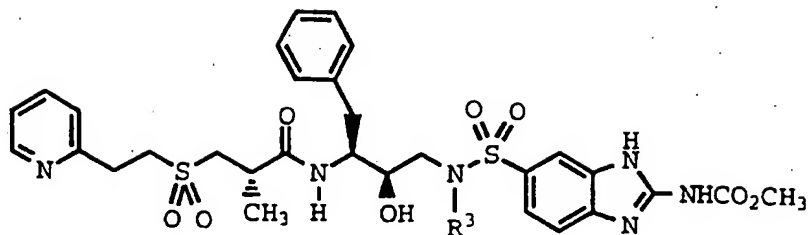
| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 11E



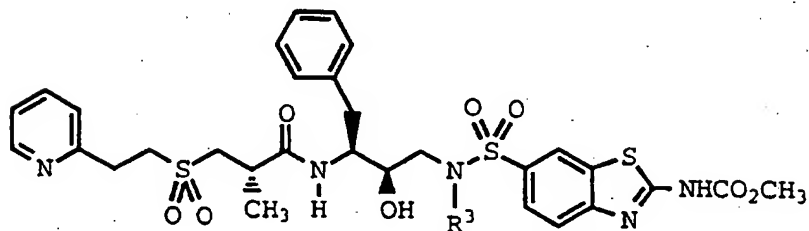
| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 11F



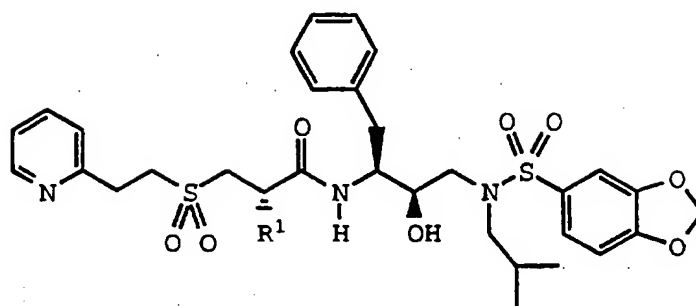
| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 11G



| Entry | R ³ | | |
|--|----------------|--|--|
| -CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH ₂ CH ₂ CH ₃ | | | |
| -CH ₂ CH(CH ₃) ₂ | | | |
| -CH ₂ CH ₂ CH(CH ₃) ₂ | | | |

TABLE 12A



5

Entry

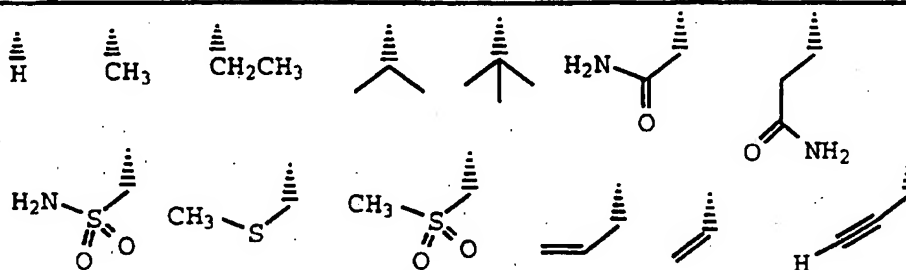
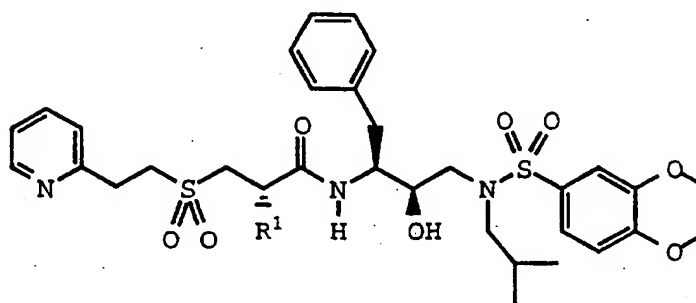
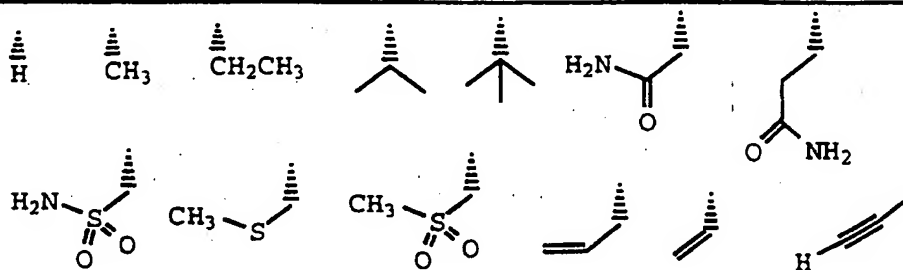
 R^1 

TABLE 12B

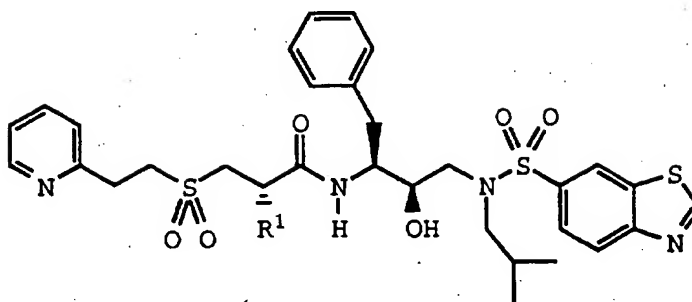
10



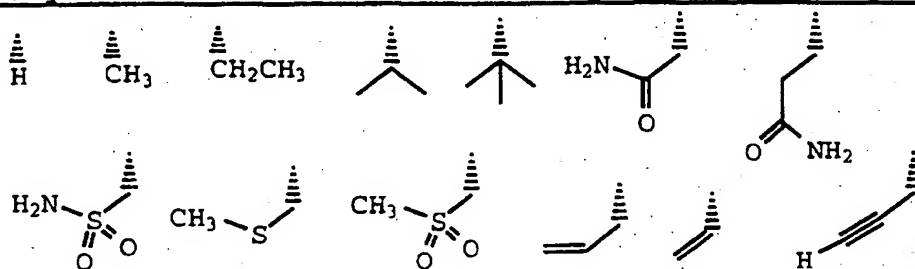
Entry

 R^1 

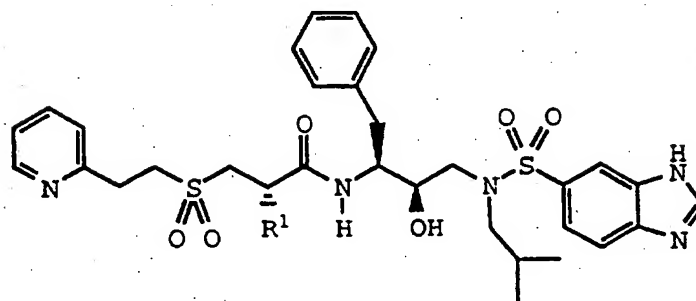
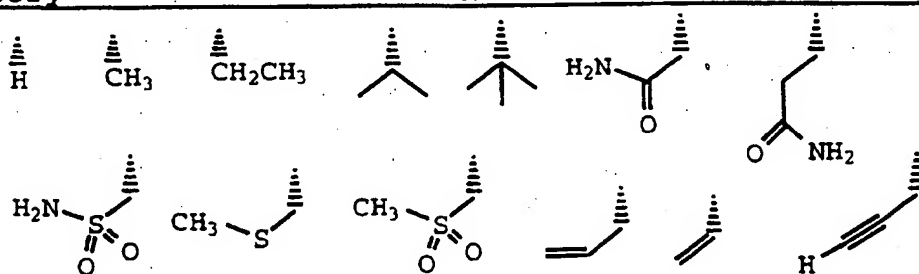
230

TABLE 12C

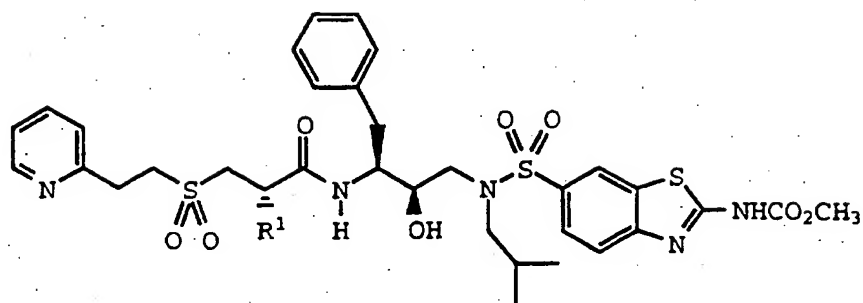
5

Entry**R¹****TABLE 12D**

10

**Entry****R¹**

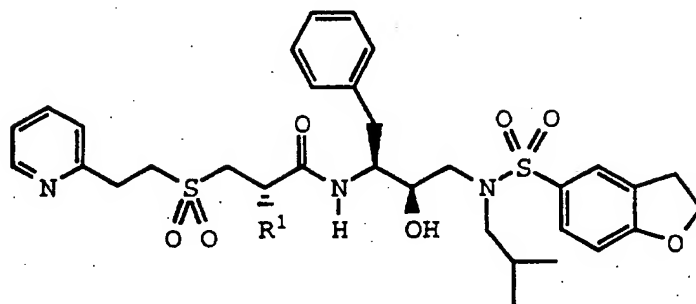
231

TABLE 12E

| 5 | Entry | R ¹ |
|---|-------|----------------|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

TABLE 12F

10



| | Entry | R ¹ |
|--|-------|----------------|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

TABLE 13A

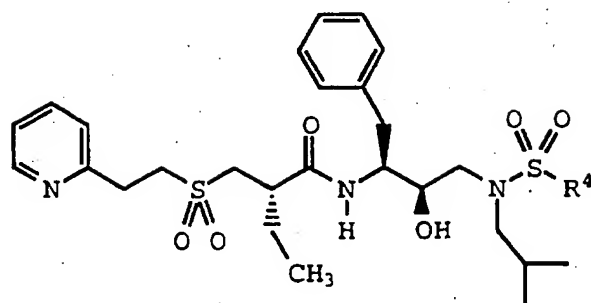
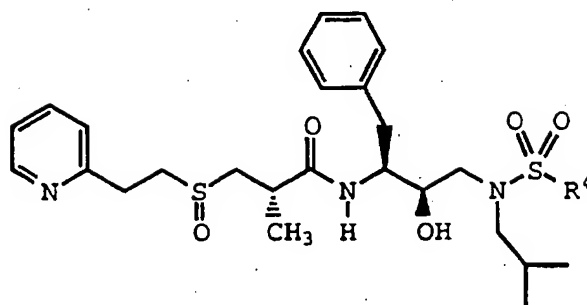
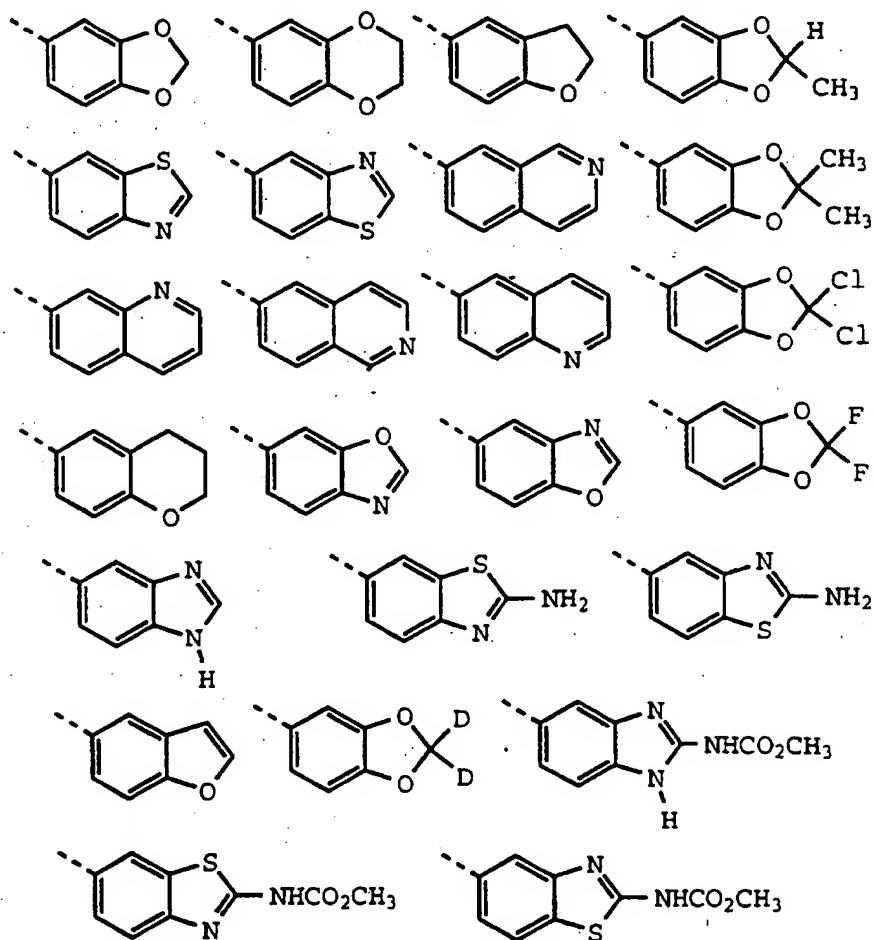
[illegible]

TABLE 13B



5

Entry

R⁴

EXAMPLE 75

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC₅₀ (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 14. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO₂)-Gln-ArgNH₂. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989))

The assay conditions are as follows:

- 15 Assay buffer: 20 mM sodium phosphate, pH 6.4
 20% glycerol
 1 mM EDTA
 1 mM DTT
 0.1% CHAPS
- 20 The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μ M. HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

30 The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10 μ l of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40 μ l of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

EXAMPLE 76

The effectiveness of various compounds were determined in the above-described enzyme assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, J. Virol. Methods, 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a CD4⁺ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2 μ g/ml). An 80 μ l volume of medium containing 1×10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100 μ l volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5×10^4 TCID₅₀ per ml (TCID₅₀ = the dose of virus that infects 50% of cells in tissue culture), and a 20 μ L volume of the virus sample (containing 1000 TCID₅₀ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

| | Cells | Drug | Virus |
|---|-------|------|-------|
| 5 | 1. + | - | - |
| | 2. + | + | - |
| | 3. + | - | + |
| | 4. + | + | + |

10 In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 µg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium
15 so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were
20 incubated at 37°C in a humidified, 5% CO₂ atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100µl sample of each cell suspension was removed for assay. A 20µL volume of a 5
25 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100µL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO₂ environment. During this incubation, MTT is metabolically reduced by living cells resulting in
30 the production in the cell of a colored formazan product. To each sample was added 100µl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular
35 Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as test compound by cytotoxicity and antiviral efficacy.

TABLE 14

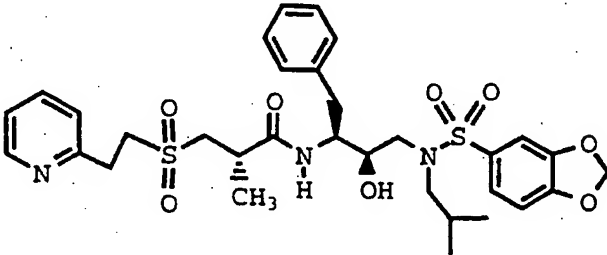
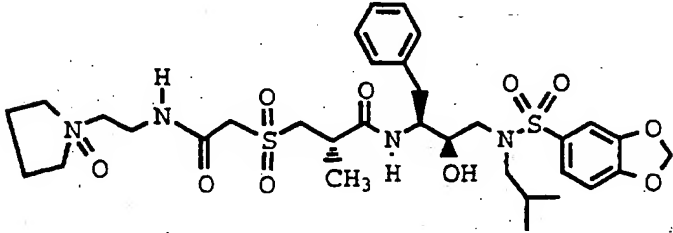
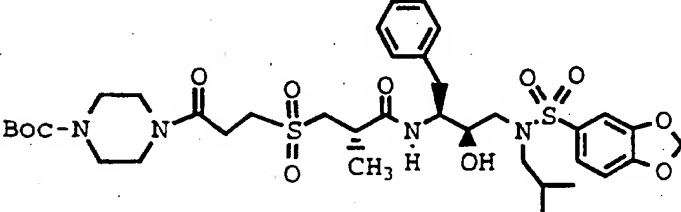
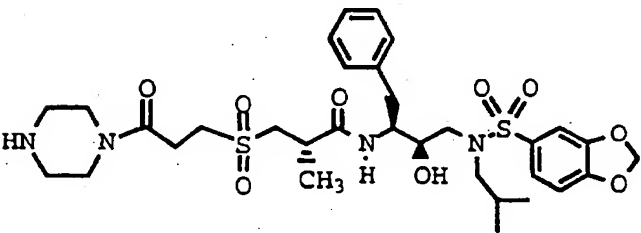
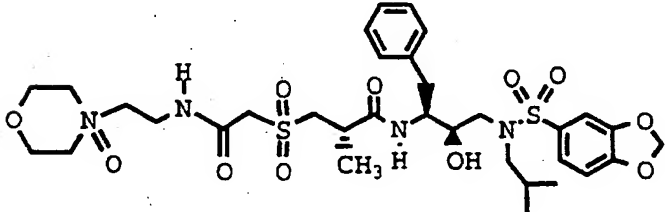
| 5 | Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|----|-------|--|--------------------------|--------------------------|
| | 1 |  | 3 | 6 |
| | 2 |  | 10 | |
| 10 | 3 |  | 4 | |
| | 4 |  | 4 | |
| | 5 |  | 10 | |

TABLE 14 (Cont'd)

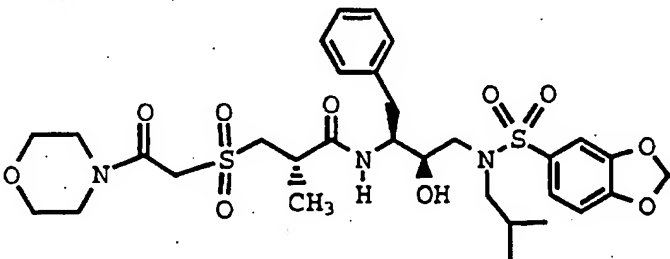
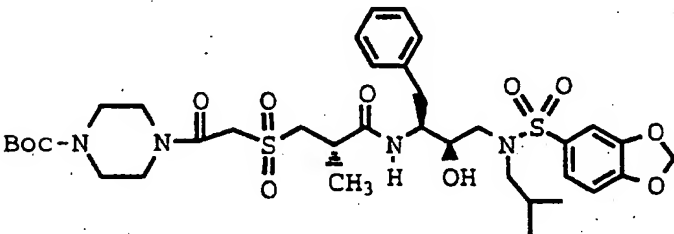
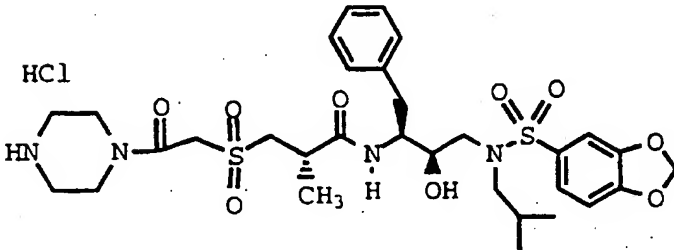
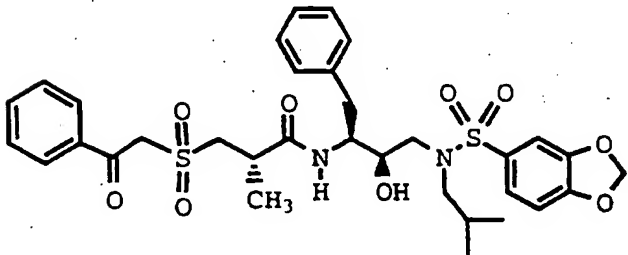
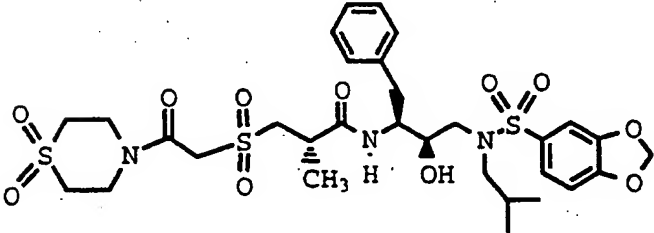
| Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|-------|--|--------------------------|--------------------------|
| 5 | | | |
| 6 |  | 24 | 123 |
| 7 |  | 7 | |
| 8 |  | 27 | |
| 10 | 9  | 4 | 39 |
| 10 |  | 16 | |

TABLE 14 (Cont'd)

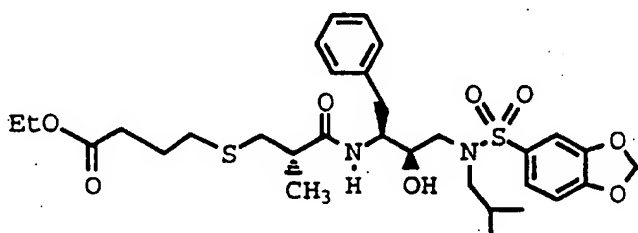
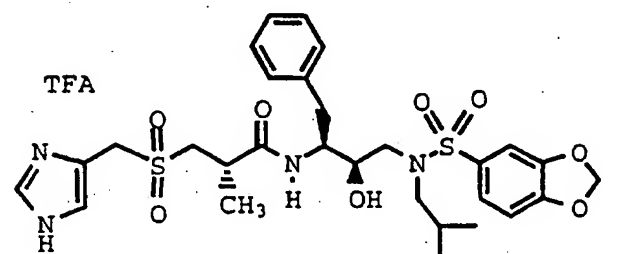
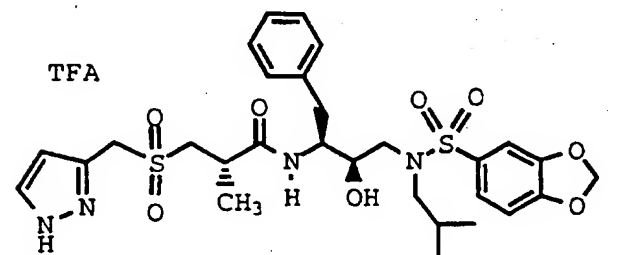
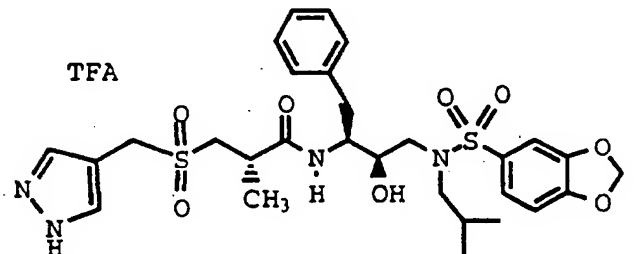
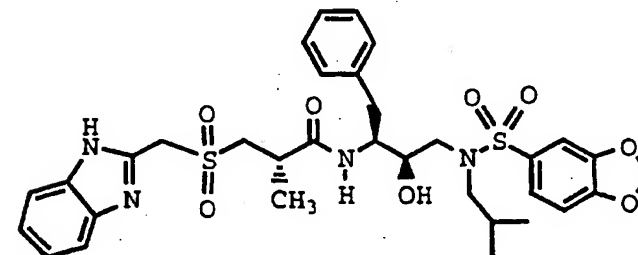
| Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|-------|--|--------------------------|--------------------------|
| 5 | | | |
| 11 |  | 22 | |
| 12 |  | 7 | 187 |
| 13 |  | 5 | 71 |
| 10 14 |  | 4 | 81 |
| 15 |  | 3 | 47 |

TABLE 14 (Cont'd)

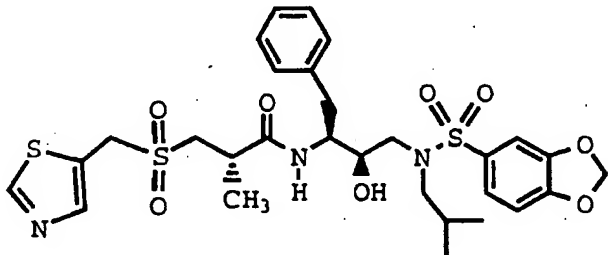
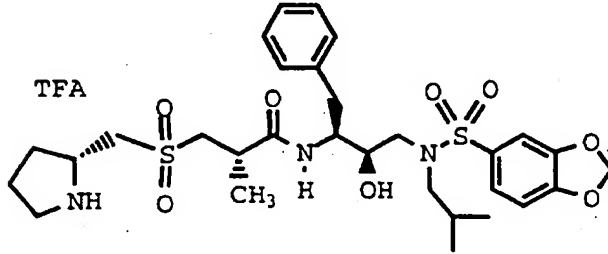
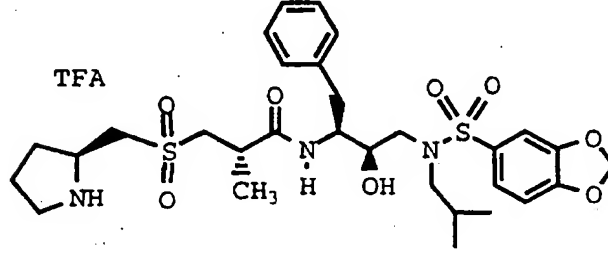
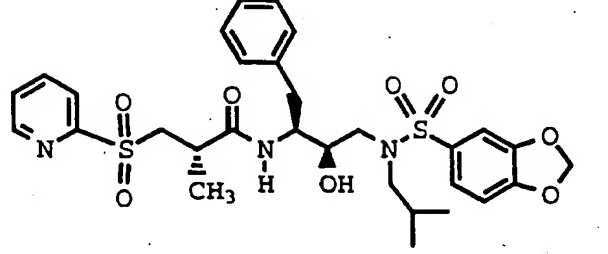
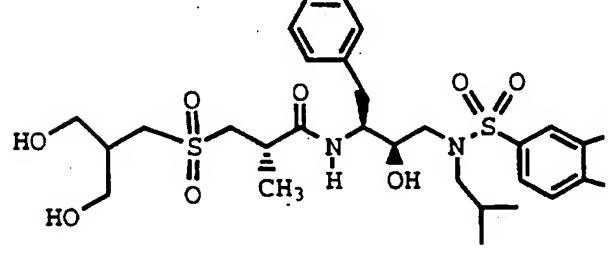
| Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|-------|--|--------------------------|--------------------------|
| 16 |  | 4 | 21 |
| 17 |  | 4 | 160 |
| 18 |  | 6 | |
| 19 |  | 11 | 174 |
| 20 |  | 4 | |

TABLE 14 (Cont'd)

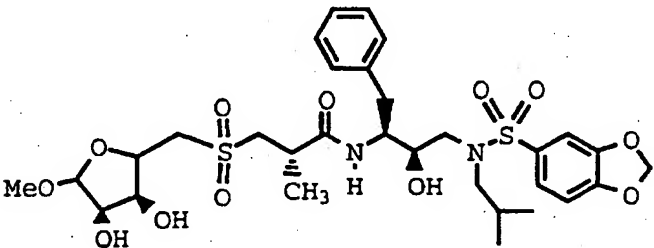
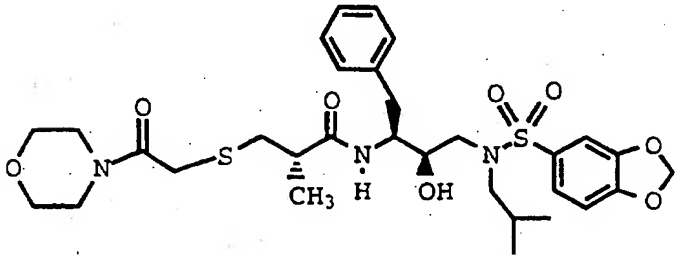
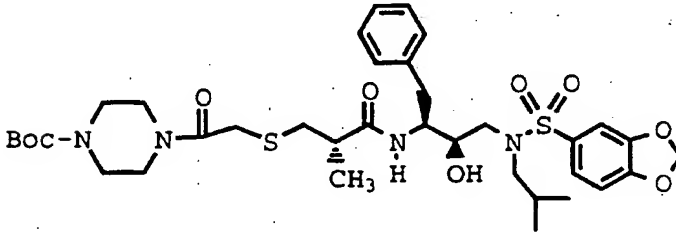
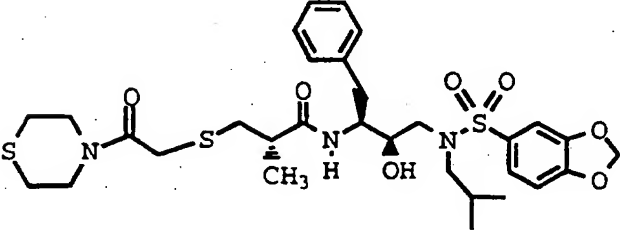
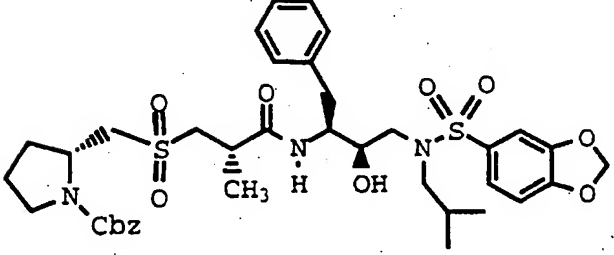
| Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|-------|--|--------------------------|--------------------------|
| 21 |  | 9 | |
| 22 |  | 63 | |
| 23 |  | 12 | |
| 24 |  | 25 | |
| 25 |  | 6 | 43 |

TABLE 14 (Cont'd)

| 5 | Entry | Compound | IC ₅₀ (nM) | EC ₅₀ (nM) |
|----|-------|----------|--------------------------|--------------------------|
| 26 | | | 16 | |
| 27 | | | 75 | |

10 The compounds of the present invention are
 effective antiviral compounds and, in particular, are
 effective retroviral inhibitors as shown above. Thus,
 the subject compounds are effective HIV protease
 inhibitors. It is contemplated that the subject
 15 compounds will also inhibit other retroviruses such as
 other lentiviruses in particular other strains of HIV,
 e.g. HIV-2, human T-cell leukemia virus, respiratory
 syncytial virus, simia immunodeficiency virus, feline
 leukemia virus, feline immuno-deficiency virus,
 20 hepadnavirus, cytomegalovirus and picornavirus. Thus,
 the subject compounds are effective in the treatment,
 prophylaxis of retroviral infections and/or the
 prevention of the spread of retroviral infections.

25 The subject compounds are also effective in
 preventing the growth of retroviruses in a solution.
 Both human and animal cell cultures, such as T-lymphocyte
 cultures, are utilized for a variety of well known
 purposes, such as research and diagnostic procedures

including calibrators and controls. Prior to and during the growth and storage of a cell culture, the subject compounds may be added to the cell culture medium at an effective concentration to prevent the unexpected or
5 undesired replication of a retrovirus that may inadvertently, unknowingly or knowingly be present in the cell culture. The virus may be present originally in the cell culture, for example HIV is known to be present in
10 human T-lymphocytes long before it is detectable in blood, or through exposure to the virus. This use of the subject compounds prevents the unknowing or inadvertent exposure of a potentially lethal retrovirus to a researcher or clinician.

15 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the
20 racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric
25 and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography
30 column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure
35 isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound.

The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

5

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

30

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

35

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile

injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile
5 injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution.
10 In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of
15 injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and
20 polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may
25 include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than
30 inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.
35

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert

diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

5

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

10

15

20

25

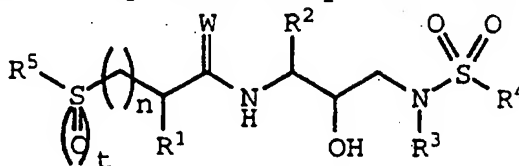
The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

30

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. Compound represented by the formula:



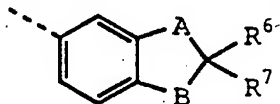
- 5 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein n and t each independently represent 0, 1 or 2; W represents O or S;

- R¹ represents hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, -CH₂CONH₂, -CH₂CH₂CONH₂, -CH₂S(O)₂NH₂, -CH₂SCH₃, -CH₂S(O)CH₃ or -CH₂S(O)₂CH₃ radicals;

- R² represents alkyl, aralkyl, alkylthioalkyl, arylthioalkyl or cycloalkylalkyl radicals;

R³ represents alkyl, cycloalkyl or cycloalkylalkyl radicals;

- 20 R⁴ represents aryl, heteroaryl or heterocyclo radicals; or R⁴ represents a radical of the formula



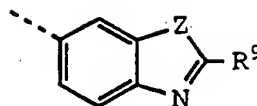
wherein A and B each independently represent O, S, SO or SO₂;

- 25 R⁶ represents deuterium, alkyl or halogen radicals; and

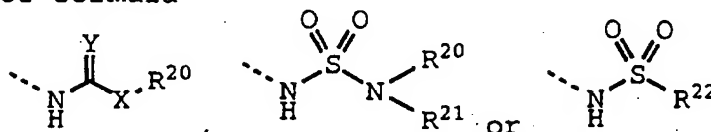
R⁷ represents hydrogen, deuterium, alkyl or halogen radicals; or

- 30 R⁴ represents a radical of the formula

249



wherein Z represents O, S or NH; and R⁹ represents a radical of formula



5 wherein Y represents O, S or NH; X represents a bond, O or NR²¹;

R²⁰ represents hydrogen, alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, heterocycloalkyl, aminoalkyl, N-mono-substituted or N,N-disubstituted aminoalkyl wherein
 10 said substituents are alkyl, aralkyl, carboxyalkyl, alkoxy-carbonylalkyl, cyanoalkyl or hydroxyalkyl radicals; or XR²⁰ represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted
 15 aminomethyl wherein said substituents are alkyl, aralkyl, carboxyalkyl, alkoxy-carbonylalkyl, cyanoalkyl or hydroxyalkyl radicals;

R²¹ represents hydrogen or alkyl radicals; or the radical
 20 of formula -NR²⁰R²¹ represents a heterocyclo radical; and

R²² represents alkyl or R²⁰R²¹N-alkyl radicals; and

R⁵ represents heteroaryl or heterocyclo radicals each of
 25 which is coupled via a ring carbon atom, or alkyl radical substituted with R¹⁰, cycloalkylamino, aralkylamino, aminoalkoxy-carbonyl, (alkylamino)alkoxy-carbonyl, (dialkylamino)alkoxy-carbonyl, (aminocarbonyl)(alkoxy-carbonyl)methyl or
 30 bis(aminocarbonyl)methyl radicals or 1 or more radicals of amino, alkylamino or dialkylamino or 2 or more radicals of hydroxy or alkoxy; and

R¹⁰ represents heteroaryl, heterocyclo, alkoxycarbonyl, arylcarbonyl, cycloalkylcarbonyl, heteroarylcarbonyl or heterocyclocarbonyl radicals; or R¹⁰ represents R¹¹R¹²N-C(O)- radical, wherein

5

R¹¹ represents heteroaryl, heterocyclo, heteroaralkyl, heterocycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cycloalkylaminoalkyl, aralkylaminoalkyl or diaminoalkyl radicals; and

10

R¹² represents hydrogen or alkyl radicals.

2. Compound of Claim 1, or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

15

R¹ represents hydrogen, alkyl of 1-5 carbon atoms, alkenyl of 2-5 carbon atoms, alkynyl of 2-5 carbon atoms, hydroxyalkyl of 1-3 carbon atoms, alkoxyalkyl of 1-3 alkyl and 1-3 alkoxy carbon atoms, cyanoalkyl of 1-3 alkyl carbon atoms, -CH₂CONH₂, -CH₂CH₂CONH₂, -CH₂S(O)₂NH₂, -CH₂SCH₃, -CH₂S(O)CH₃ or -CH₂S(O)₂CH₃ radicals;

20

R² represents radicals of alkyl of 1-5 carbon atoms, aralkyl of 1-3 alkyl carbon atoms, alkylthioalkyl of 1-3 alkyl carbon atoms, arylthioalkyl of 1-3 alkyl carbon atoms or cycloalkylalkyl of 1-3 alkyl carbon atoms and 3-6 ring member carbon atoms;

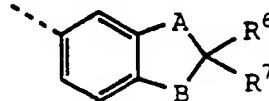
25

R³ represents radicals of alkyl of 1-5 carbon atoms, cycloalkyl of 5-8 ring members or cycloalkylmethyl of 3-6 ring members;

30

R⁴ represents aryl, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals; or R⁴ represents a radical of the formula

35

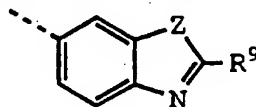


wherein A and B each independently represent O, S, SO or SO₂;

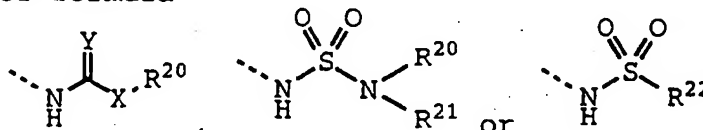
R⁶ represents deuterium, alkyl of 1-5 carbon atoms, fluoro or chloro radicals; and

R⁷ represents hydrogen, deuterium, alkyl of 1-3 carbon atoms, fluoro or chloro radicals; or

R⁴ represents a radical of the formula



wherein Z represents O, S or NH; and R⁹ represents a radical of formula



wherein Y represents O, S or NH; -X represents a bond, O or NR²¹;

R²⁰ represents radicals of hydrogen, alkyl of 1 to 5 carbon atoms, alkenyl of 2 to 5 carbon atoms, alkynyl of 2 to 5 carbon atoms, aralkyl of 1 to 5 alkyl carbon atoms, heteroaralkyl of 5 to 6 ring members and 1 to 5 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 5 alkyl carbon atoms, aminoalkyl of 2 to 5 carbon atoms, N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 5 alkyl carbon atoms wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms, aralkyl of 1 to 3 alkyl carbon atoms, carboxyalkyl of 1 to 5 carbon atoms, alkoxycarbonylalkyl of 1 to 5 alkyl carbon atoms, cyanoalkyl of 1 to 5 carbon atoms or hydroxyalkyl of 2 to 5 carbon atoms; or XR²⁰ represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted aminomethyl wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms, aralkyl of 1 to 3 alkyl carbon atoms, carboxyalkyl of 1 to 5 carbon atoms,

alkoxycarbonylalkyl of 1 to 5 alkyl carbon atoms,
cyanoalkyl of 1 to 5 carbon atoms or hydroxyalkyl of 2 to
5 carbon atoms;

5 R²¹ represents radicals of hydrogen or alkyl of 1 to 3
carbon atoms; or the radical of formula -NR²⁰R²¹
represents a 5 to 6 ring member heterocyclo radical; and

R²² represents alkyl or R²⁰R²¹N-alkyl radicals wherein
10 alkyl is 1 to 3 carbon atoms; and

R⁵ represents 5 to 6 ring member heteroaryl, 5 to 6 ring
member heterocyclo, benzo fused 5 to 6 ring member
heteroaryl or benzo fused 5 to 6 ring member heterocyclo
15 radicals each of which is coupled via a ring carbon atom,
or alkyl radical of 3-8 carbon atoms substituted with 2-5
radicals of hydroxy or alkoxy of 1-3 carbon atoms or 2-3
radicals of amino, alkylamino of 1-3 carbon atoms or
dialkylamino of 1-3 alkyl carbon atoms, or alkyl radical
20 of 1-5 carbon atoms substituted with R¹⁰, or alkyl
radical of 2-4 carbon atoms substituted with radicals of
amino, alkylamino of 1-3 carbon atoms, dialkylamino of 1-
3 alkyl carbon atoms, cycloalkylamino of 3-6 ring carbon
atoms, aralkylamino of 1-3 alkyl carbon atoms,
25 aminoalkoxycarbonyl of 2-5 alkoxy carbon atoms,
(alkylamino)alkoxycarbonyl of 1-3 alkyl carbon atoms and
2-5 alkoxy carbon atoms, (dialkylamino)alkoxycarbonyl of
1-3 alkyl carbon atoms and of 2-5 alkoxy carbon atoms,
(aminocarbonyl)(alkoxycarbonyl)methyl of 1-3 alkoxy
30 carbon atoms or bis(aminocarbonyl)methyl radicals; and

R¹⁰ represents alkoxycarbonyl of 1-5 alkoxy carbon atoms,
arylcarbonyl, 3-6 ring membered cycloalkylcarbonyl, benzo
fused 3-6 ring membered cycloalkylcarbonyl, 5 to 6 ring
35 member heteroaryl, 5 to 6 ring member heterocyclo, benzo
fused 5 to 6 ring member heteroaryl, benzo fused 5 to 6
ring member heterocyclo, 5 to 6 ring member

heteroarylcarbonyl, 5 to 6 ring member
heterocyclocarbonyl, benzo fused 5 to 6 ring member
heteroarylcarbonyl or benzo fused 5 to 6 ring member
heterocyclocarbonyl radicals; or R¹⁰ represents R¹¹R¹²N-
5 C(O)- radical, wherein

R¹¹ represents 5 to 6 ring member heteroaryl, 5 to 6 ring
member heterocyclo, benzo fused 5 to 6 ring member
heteroaryl or benzo fused 5 to 6 ring member heterocyclo
10 radicals, or alkyl radical of 1-5 carbon atoms
substituted with 5 to 6 ring member heteroaryl, 5 to 6
ring member heterocyclo, benzo fused 5 to 6 ring member
heteroaryl or benzo fused 5 to 6 ring member heterocyclo
radicals, or diaminoalkyl radical of 3-5 carbon atoms, or
15 alkyl radical of 2-4 carbon atoms substituted with
radicals of amino, alkylamino of 1-3 carbon atoms,
dialkylamino of 1-3 alkyl carbon atoms, cycloalkylamino
of 3-6 ring carbon atoms or aralkylamino of 1-3 alkyl
carbon atoms; and

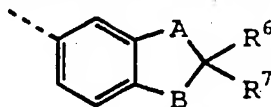
20 R¹² represents radicals of hydrogen or alkyl of 1-3
carbon atoms.

3. Compound of Claim 2, or a pharmaceutically
25 acceptable salt, prodrug or ester thereof, wherein n
represents 1; t represents 1 or 2; W represents O;

R¹ represents hydrogen, alkyl of 1-3 carbon atoms,
alkenyl of 2-3 carbon atoms, alkynyl of 2-3 carbon atoms
30 or cyanomethyl radicals;

R² represents radicals of alkyl of 3-5 carbon atoms,
arylmethyl, alkylthioalkyl of 1-3 alkyl carbon atoms,
arylthiomethyl or cycloalkylmethyl of 5-6 ring member
35 carbon atoms;

R⁴ represents aryl, benzo fused 5 to 6 ring member heteroaryl or benzo fused 5 to 6 ring member heterocyclo radicals; or R⁴ represents a radical of the formula

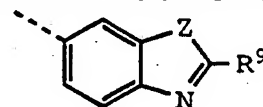


5 wherein A and B each represent O;

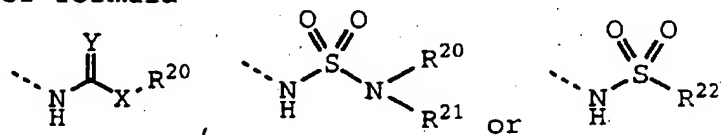
R⁶ represents deuterium, methyl, ethyl, propyl, isopropyl or fluoro radicals; and

10 R⁷ represents hydrogen, deuterium, methyl or fluoro radicals; or

R⁴ represents a radical of the formula



15 wherein Z represents O, S or NH; and R⁹ represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR²¹;

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R²⁰ represents hydrogen, alkyl of 1 to 5 carbon atoms, phenylalkyl of 1 to 3 alkyl carbon atoms, heterocycloalkyl of 5 to 6 ring members and 1 to 3 alkyl carbon atoms, or N-mono-substituted or N,N-disubstituted aminoalkyl of 2 to 3 carbon atoms wherein said substituents are alkyl radicals of 1 to 3 carbon atoms; or XR²⁰ represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted aminomethyl wherein said substituents are radicals of alkyl of 1 to 3 carbon atoms;

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R²¹ represents hydrogen or methyl radicals; or the radical of formula -NR²⁰R²¹ represents pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, morpholinyl or thiomorpholinyl radicals; and

R²² represents alkyl radical of 1 to 3 carbon atoms; and

R⁵ represents a 5 to 6 ring member heteroaryl radical which is coupled via a ring carbon atom, or alkyl radical of 1-5 carbon atoms substituted with R¹⁰, or alkyl radical of 3-8 carbon atoms substituted with 2-5 hydroxy radicals; and

R¹⁰ represents alkoxycarbonyl of 1-4 alkoxy carbon atoms, arylcarbonyl, 5 to 6 ring member heteroaryl, 5 to 6 ring member heterocyclo, benzo fused 5 to 6 ring member heteroaryl, 5 to 6 ring member heteroarylcarbonyl or 5 to 6 ring member heterocyclocarbonyl radicals; or R¹⁰ represents R¹¹R¹²N-C(O)- radical, wherein

R¹¹ represents alkyl radical of 1-3 carbon atoms substituted with 5 to 6 ring member heteroaryl or 5 to 6 ring member heterocyclo radicals; and

R¹² represents hydrogen or methyl radicals.

4. Compound of Claim 3 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R¹ represents hydrogen, methyl, ethyl or cyanomethyl radicals;

R² represents isobutyl, n-butyl, CH₃SCH₂CH₂-, benzyl, phenylthiomethyl, (2-naphthylthio)methyl, 4-methoxy phenylmethyl, 4-hydroxyphenylmethyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals;

R³ represents propyl, isoamyl, isobutyl, butyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexyl or cycloheptyl radicals;

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R²⁰ represents hydrogen, methyl, ethyl, propyl, isopropyl, isobutyl, benzyl, 2-(1-pyrrolidinyl)ethyl, 2-(1-piperidinyl)ethyl, 2-(1-piperazinyl)ethyl, 2-(4-methylpiperazin-1-yl)ethyl, 2-(4-morpholinyl)ethyl, 2-(4-thiomorpholinyl)ethyl or 2-(N,N-dimethylamino)ethyl radicals; or XR²⁰ represents hydroxymethyl or aminomethyl radicals;

10

R²¹ represents a hydrogen radical; and

15

R¹⁰ represents ethoxycarbonyl, tert-butoxycarbonyl, benzoyl, naphthoyl, aminophenylcarbonyl, amidinophenylcarbonyl, pyridylcarbonyl, thiazolylcarbonyl, imidazolylcarbonyl, pyrazolylcarbonyl, pyrimidinylcarbonyl, pyrazinylcarbonyl, benzimidazolylcarbonyl, indolylcarbonyl, pyrrolylcarbonyl, quinolinylcarbonyl, pyrrolylcarbonyl, pyrrolidinylcarbonyl, 1-(benzyloxycarbonyl)pyrrolidinylcarbonyl, piperidinylcarbonyl, 1-(benzyloxycarbonyl)piperidinylcarbonyl, piperazinylcarbonyl, 4-methylpiperazinylcarbonyl, 4-benzylpiperazinylcarbonyl, 4-(tert-butoxycarbonyl)piperazinylcarbonyl, morpholinylcarbonyl, thiomorpholinylcarbonyl, 1,1-dioxothiomorpholinylcarbonyl, pyrrolidinyl, 1-oxopyrrolidin-1-yl, 1-(benzyloxycarbonyl)pyrrolidinyl, piperidinyl, 1-oxopiperidin-1-yl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, 4-(tert-butoxycarbonyl)piperazinyl, morpholinyl, 4-oxomorpholin-4-yl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, 1,1,4-trioxothiomorpholin-4-yl, thiazolyl, oxazolyl, pyrrolyl, furyl, imidazolyl, pyrazolyl, isoxazolyl, thienyl,

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pyrimidinyl, pyrazinyl, pyridyl, quinolinyl, quinolonyl, N-methylquinolonyl, benzothiazolyl, benzoxazolyl, benzofuranyl, benzimidazolyl, indolyl, dihydroxytetrahydrofuran-5-yl, trihydroxytetrahydrofuran-5-yl, 2-methoxydihydroxytetrahydrofuran-5-yl, trihydroxytetrahydrofuranyl, 2-(hydroxymethyl)dihydroxytetrahydrofuran-5-yl, 2-methoxytrihydroxytetrahydropyran-6-yl or tetrahydroxytetrahydropyran-6-yl radicals; or R¹⁰ represents R¹¹R¹²N-C(O)- radical, wherein

R¹¹ represents 2-pyrrolidinylmethyl, 2-(1-pyrrolidinyl)ethyl, 2-(1-oxopyrrolidin-1-yl)ethyl, 2-(1-piperidinyl)ethyl, 2-(1-oxopiperidin-1-yl)ethyl, 2-(4-morpholinyl)ethyl, 2-(4-oxomorpholin-4-yl)ethyl, 2-(4-thiomorpholinyl)ethyl, 2-(1,1-dioxothiomorpholin-4-yl)ethyl or 2-(1,1,4-trioxothiomorpholin-4-yl)ethyl radicals; and

R¹² represents a hydrogen radical.

5. Compound of Claim 4 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R¹ represents methyl or ethyl radicals;

R² represents benzyl, 4-fluorophenylmethyl or cyclohexylmethyl radicals;

R⁴ represents phenyl, 2-naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, 3,4-dimethoxyphenyl, 3-aminophenyl, 4-aminophenyl, benzothiazol-5-yl, benzothiazol-6-yl, 2-amino-benzothiazol-5-yl, 2-(methoxycarbonylamino)benzothiazol-5-yl, 2-amino-benzothiazol-6-yl, 2-(methoxycarbonylamino)benzothiazol-6-yl, 5-benzoxazolyl, 6-benzoxazolyl, 6-benzopyranyl, 3,4-dihydrobenzopyran-6-yl, 7-benzopyranyl, 3,4-dihydrobenzopyran-7-yl, 2,3-

dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 5-benzimidazolyl, 2-(methoxycarbonylamino)benzimidazol-5-yl, 6-quinolinyl, 7-quinolinyl, 6-isoquinolinyl or 7-isoquinolinyl radicals; and

R⁵ represents 2-pyridyl, ethoxycarbonylpropyl, benzoylmethyl, morpholinylcarbonylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylmethyl, piperazinylcarbonylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylethyl, piperazinylcarbonylethyl, thiomorpholinylcarbonylmethyl, 1,1-dioxothiomorpholinylcarbonylmethyl, imidazolylethyl, imidazolylcarbonylmethyl, pyrazolylethyl, thiazolylethyl, imidazolylmethyl, pyrazolylmethyl, thiazolylmethyl, benzimidazolylmethyl, pyridylethyl, pyridylcarbonylmethyl, pyrrolidinylmethyl, 1-(benzyloxycarbonyl)pyrrolidinylmethyl, 5-methoxy-3,4-dihydroxy-tetrahydrofuranylmethyl, N-[2-(4-oxomorpholin-4-yl)ethyl]aminocarbonylmethyl, N-[2-(1-pyrrolidinyl)ethyl]aminocarbonylmethyl, N-[2-(1-pyrrolidinyl)ethyl]aminocarbonylethyl, N-[2-(1-oxopyrrolidin-1-yl)ethyl]aminocarbonylmethyl, 2,2-bis(hydroxymethyl)ethyl, 2,2,2-tris(hydroxymethyl)ethyl, 2-[(2-aminoethyl)aminocarbonyl]ethyl or 2-[(2-methylamino)ethyl]aminocarbonyl]ethyl radicals.

6. Compound of Claim 5 or a pharmaceutically acceptable salt, prodrug or ester thereof, wherein

R¹ represents a methyl radical;

R² represents benzyl;

R³ represents isobutyl or cyclopentylmethyl radicals;

R⁴ represents phenyl, 2-naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,3-benzodioxol-5-yl, 2-methyl-1,3-benzodioxol-5-yl, 2,2-dimethyl-1,3-benzodioxol-5-yl, 2,2-dideutero-1,3-benzodioxol-5-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2-(methoxycarbonylamino) benzothiazol-5-yl, 2-(methoxycarbonylamino)benzothiazol-6-yl or 2-(methoxycarbonylamino)benzimidazol-5-yl radicals; and

R⁵ represents benzoylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylmethyl, 4-(tert-butoxycarbonyl)piperazinylcarbonylethyl, piperazinylcarbonylethyl, imidazolylethyl, pyrazolylethyl, thiazolylethyl, imidazolylmethyl, pyrazolylmethyl, thiazolylmethyl, pyridylethyl, pyridylcarbonylmethyl, pyrrolidinylmethyl or 1-(benzyloxycarbonyl)pyrrolidinylmethyl radicals.

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7. Compound of Claim 1 wherein said pharmaceutically acceptable salt is hydrochloric acid salt, sulphuric acid salt, phosphoric acid salt, oxalic acid salt, maleic acid salt, succinic acid salt, citric acid salt or methanesulfonic acid salt.

8. Compound of Claim 7 wherein said pharmaceutically acceptable salt is hydrochloric acid salt, oxalic acid salt, citric acid salt or methanesulfonic acid salt.

9. Compound of Claim 1 which is

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;

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- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 40 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 45 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 50 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(4-pyridylcarbonylmethyl)sulfonyl]propanamide;
- 55 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;

- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;
- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(3-pyrazolylmethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(benzoylmethyl)sulfonyl]propanamide;
- 40 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- 45 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- 50 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;
- 55 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(5-thiazolylmethyl)sulfonyl]propanamide;

- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-2-ylethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 40 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-3-ylethyl)sulfonyl]propanamide;
- 45 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 50 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 55 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;

- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-pyrid-4-ylethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(1-(benzyloxycarbonyl)pyrrolidin-2S-ylmethyl)sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- 40 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- 45 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- 50 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(1-piperazinylcarbonyl)ethyl)sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;

- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 5 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 10 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 15 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(2-(2-aminoethylaminocarbonyl)ethyl)sulfonyl]propanamide;
- 20 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- 25 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- 30 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[[2-(hydroxymethyl)-3-hydroxypropyl]sulfonyl]propanamide;
- 35 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,3-benzodioxol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;
- 40 N-[2R-hydroxy-3-[(2-methylpropyl)[(1,4-benzodioxan-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;
- 45 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-6-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide;
- 50 N-[2R-hydroxy-3-[(2-methylpropyl)[(benzothiazol-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide; or
- 55 N-[2R-hydroxy-3-[(2-methylpropyl)[(2,3-dihydrobenzofuran-5-yl)sulfonyl]amino]-1S-(phenylmethyl)propyl]-2S-methyl-3-[(pyrrolidin-2R-ylmethyl)sulfonyl]propanamide.

10. Composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

5 11. Method of inhibiting a retroviral protease comprising administering an effective amount of a compound of Claim 1.

10 12. Method of Claim 11 wherein the retroviral protease is HIV protease.

15 13. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 10.

14. Method of Claim 13 wherein the retroviral infection is HIV infection.

20 15. Method of preventing replication of a retrovirus comprising administering an effective amount of a compound of Claim 1.

16. Method of Claim 15 wherein the retrovirus is HIV.

25 17. Method of preventing replication of a retrovirus *in vitro* comprising administering an effective amount of a compound of Claim 1.

30 18. Method of Claim 17 wherein the retrovirus is HIV.

19. Method of treating AIDS comprising administering an effective amount of a composition of Claim 10.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/17771

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D405/12 A61K31/36 C07D417/12 C07D317/62 C07H7/06
C07D319/18 C07D277/62 C07D307/79

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X,Y | WO 94 04493 A (SEARLE & CO ;MONSANTO CO (US); VAZQUEZ MICHAEL L (US); MUELLER RIC) 3 March 1994 cited in the application see the whole document, in particular pages 67 and 77 --- | 1-19 |
| Y | WO 95 06030 A (SEARLE & CO ;MONSANTO CO (US); VAZQUEZ MICHAEL L (US); MUELLER RIC) 2 March 1995 see the whole document --- | 1-19 |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

18 February 1997

Date of mailing of the international search report

14. 03. 97

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INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/US 96/17771

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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